



## Clinical trial results:

### A 1-week, open-label, multi-center study to explore conduction abnormalities during first dose administration of fingolimod in patients with relapsing-remitting multiple sclerosis (START)

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2012-000653-32   |
| Trial protocol           | DE               |
| Global end of trial date | 12 December 2016 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 23 December 2017 |
| First version publication date | 23 December 2017 |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CFTY720DDE17 |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01585298 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

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

Notes:

#### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 12 December 2016 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 12 December 2016 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the incidence of patients with bradycardia (heart rate < 45 beats per min) and bradyarrhythmic ECG events during 6-hour monitoring period as measured by heart rate and second and third-degree AV blocks after treatment initiation of fingolimod 0.5 mg.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 29 June 2012 |
| 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 | Germany: 6998 |
| Worldwide total number of subjects   | 6998          |
| EEA total number of subjects         | 6998          |

Notes:

### Subjects enrolled per age group

|                                           |      |
|-------------------------------------------|------|
| In utero                                  | 0    |
| Preterm newborn - gestational age < 37 wk | 0    |
| Newborns (0-27 days)                      | 0    |
| Infants and toddlers (28 days-23 months)  | 0    |
| Children (2-11 years)                     | 0    |
| Adolescents (12-17 years)                 | 0    |
| Adults (18-64 years)                      | 6957 |
| From 65 to 84 years                       | 41   |
| 85 years and over                         | 0    |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

All participants received open-label fingolimod.

### Period 1

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

### Arms

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

Arm description:

Fingolimod 0.5 mg by mouth once daily for 7 days.

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

Dosage and administration details:

Fingolimod 0.5 mg by mouth once daily for 7 days.

| Number of subjects in period 1       | Fingolimod |
|--------------------------------------|------------|
| Started                              | 6998       |
| Completed                            | 6961       |
| Not completed                        | 37         |
| Consent withdrawn by subject         | 4          |
| Abnormal test procedure results      | 1          |
| Study completion was not documented. | 1          |
| Adverse event, non-fatal             | 24         |
| Protocol deviation                   | 1          |
| Administrative problems              | 4          |
| Lost to follow-up                    | 2          |

## Baseline characteristics

### Reporting groups

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

Reporting group description:

Fingolimod 0.5 mg by mouth once daily for 7 days.

| Reporting group values                             | Fingolimod | Total |  |
|----------------------------------------------------|------------|-------|--|
| Number of subjects                                 | 6998       | 6998  |  |
| Age categorical                                    |            |       |  |
| Units: Subjects                                    |            |       |  |
| In utero                                           | 0          | 0     |  |
| Preterm newborn infants (gestational age < 37 wks) | 0          | 0     |  |
| Newborns (0-27 days)                               | 0          | 0     |  |
| Infants and toddlers (28 days-23 months)           | 0          | 0     |  |
| Children (2-11 years)                              | 0          | 0     |  |
| Adolescents (12-17 years)                          | 0          | 0     |  |
| Adults (18-64 years)                               | 6957       | 6957  |  |
| From 65-84 years                                   | 41         | 41    |  |
| 85 years and over                                  | 0          | 0     |  |
| Age Continuous                                     |            |       |  |
| Units: Years                                       |            |       |  |
| arithmetic mean                                    | 39.2       |       |  |
| standard deviation                                 | ± 10.52    | -     |  |
| Gender, Male/Female                                |            |       |  |
| Units: Subjects                                    |            |       |  |
| Female                                             | 4924       | 4924  |  |
| Male                                               | 2074       | 2074  |  |

## End points

### End points reporting groups

|                                                                                   |            |
|-----------------------------------------------------------------------------------|------------|
| Reporting group title                                                             | Fingolimod |
| Reporting group description:<br>Fingolimod 0.5 mg by mouth once daily for 7 days. |            |

### Primary: Number of participants with 2nd or 3rd degree AV block

|                 |                                                                       |
|-----------------|-----------------------------------------------------------------------|
| End point title | Number of participants with 2nd or 3rd degree AV block <sup>[1]</sup> |
|-----------------|-----------------------------------------------------------------------|

End point description:

Number of participants with 2nd or 3rd degree AV block in ECG during first dose observation. Participants can simultaneously experience both types of AV blocks. Two patients of the safety analysis set discontinued the study without having received treatment, but safety information was collected on these two patients.

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

End point timeframe:

baseline during 6 hour monitoring post dose

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: Statistical analysis does not apply to this end point.

| End point values                          | Fingolimod      |  |  |  |
|-------------------------------------------|-----------------|--|--|--|
| Subject group type                        | Reporting group |  |  |  |
| Number of subjects analysed               | 6998            |  |  |  |
| Units: Participants                       |                 |  |  |  |
| Any AV block II degree or higher          | 120             |  |  |  |
| AV block II degree: Mobitz type I degree  | 117             |  |  |  |
| AV block II degree: Mobitz type II degree | 0               |  |  |  |
| AV block II degree: 2:1                   | 43              |  |  |  |
| AV block III degree                       | 1               |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Number of patients with heart rate below 45 beats per minute (BPM)

|                 |                                                                                   |
|-----------------|-----------------------------------------------------------------------------------|
| End point title | Number of patients with heart rate below 45 beats per minute (BPM) <sup>[2]</sup> |
|-----------------|-----------------------------------------------------------------------------------|

End point description:

Number of patients with heart rate below 45 beats bpm in ECG during first dose observation. Two patients of the safety analysis set discontinued the study without having received treatment, but safety information was collected on these two patients.

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

End point timeframe:

baseline during 6 hour monitoring post dose

Notes:

[2] - 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: Statistical analysis does not apply to this end point.

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | Fingolimod      |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 6998            |  |  |  |
| Units: Participants         | 63              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants with prolonged QTc interval (Friderica)

|                 |                                                                |
|-----------------|----------------------------------------------------------------|
| End point title | Number of participants with prolonged QTc interval (Friderica) |
|-----------------|----------------------------------------------------------------|

End point description:

Number of patients with conduction abnormalities such as QT prolongation, first degree AV block during treatment initiation. Two patients of the safety analysis set discontinued the study without having received treatment, but safety information was collected on these two patients.

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

End point timeframe:

baseline post-dose

|                                                  |                 |  |  |  |
|--------------------------------------------------|-----------------|--|--|--|
| <b>End point values</b>                          | Fingolimod      |  |  |  |
| Subject group type                               | Reporting group |  |  |  |
| Number of subjects analysed                      | 6844            |  |  |  |
| Units: Participants                              |                 |  |  |  |
| Female, QTcFridericia Interval > 470 ms (n=4808) | 7               |  |  |  |
| Male, QTcF Interval > 450 ms (n=2036)            | 6               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants with bradyarrhythmic electrocardiogram (ECG) events

|                 |                                                                            |
|-----------------|----------------------------------------------------------------------------|
| End point title | Number of participants with bradyarrhythmic electrocardiogram (ECG) events |
|-----------------|----------------------------------------------------------------------------|

End point description:

The number of participants with bradyarrhythmic electrocardiogram (ECG) events was assessed. Bradyarrhythmic ECG events are defined as QTc Fridericia time > 450 ms for males and > 470 ms for females. Two patients of the safety analysis set discontinued the study without having received treatment, but safety information was collected on these two patients.

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

End point timeframe:

up to day 7

| End point values            | Fingolimod      |  |  |  |
|-----------------------------|-----------------|--|--|--|
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 6998            |  |  |  |
| Units: Participants         | 26              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of patients with cardiac adverse events

|                 |                                                |
|-----------------|------------------------------------------------|
| End point title | Number of patients with cardiac adverse events |
|-----------------|------------------------------------------------|

End point description:

The number of participants with the occurrence of subsequent cardiac adverse events (AEs) and serious cardiac AEs during study was assessed. Cardiac events were defined as the following Medical Dictionary for Regulatory Activities (MedDRA) preferred terms: angina pectoris, chest discomfort, dizziness, dyspnoea, dyspnoea exertional, fatigue, palpitations, syncope, vertigo, vertigo positional and vision blurred. Two patients of the safety analysis set discontinued the study without having received treatment, but safety information was collected on these two patients.

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

End point timeframe:

7 days

| End point values            | Fingolimod      |  |  |  |
|-----------------------------|-----------------|--|--|--|
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 6998            |  |  |  |
| Units: Participants         |                 |  |  |  |
| Cardiac events              | 489             |  |  |  |
| Serious cardiac AEs         | 9               |  |  |  |

## Statistical analyses





## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

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

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 19.1   |

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Fingolimod 0.5 mg |
|-----------------------|-------------------|

Reporting group description:

Fingolimod 0.5 mg

| Serious adverse events                                              | Fingolimod 0.5 mg  |  |  |
|---------------------------------------------------------------------|--------------------|--|--|
| Total subjects affected by serious adverse events                   |                    |  |  |
| subjects affected / exposed                                         | 160 / 6998 (2.29%) |  |  |
| number of deaths (all causes)                                       | 0                  |  |  |
| number of deaths resulting from adverse events                      | 0                  |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |  |  |
| Brain neoplasm benign                                               |                    |  |  |
| subjects affected / exposed                                         | 1 / 6998 (0.01%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1              |  |  |
| deaths causally related to treatment / all                          | 0 / 0              |  |  |
| Vascular disorders                                                  |                    |  |  |
| Blood pressure fluctuation                                          |                    |  |  |
| subjects affected / exposed                                         | 1 / 6998 (0.01%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1              |  |  |
| deaths causally related to treatment / all                          | 0 / 0              |  |  |
| Hypertension                                                        |                    |  |  |
| subjects affected / exposed                                         | 3 / 6998 (0.04%)   |  |  |
| occurrences causally related to treatment / all                     | 2 / 3              |  |  |
| deaths causally related to treatment / all                          | 0 / 0              |  |  |
| Hypertensive crisis                                                 |                    |  |  |

|                                                      |                  |  |  |
|------------------------------------------------------|------------------|--|--|
| subjects affected / exposed                          | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| Pregnancy, puerperium and perinatal conditions       |                  |  |  |
| Unintended pregnancy                                 |                  |  |  |
| subjects affected / exposed                          | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| General disorders and administration site conditions |                  |  |  |
| Fatigue                                              |                  |  |  |
| subjects affected / exposed                          | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| General physical health deterioration                |                  |  |  |
| subjects affected / exposed                          | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| Malaise                                              |                  |  |  |
| subjects affected / exposed                          | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| Non-cardiac chest pain                               |                  |  |  |
| subjects affected / exposed                          | 2 / 6998 (0.03%) |  |  |
| occurrences causally related to treatment / all      | 1 / 2            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| Pyrexia                                              |                  |  |  |
| subjects affected / exposed                          | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| Respiratory, thoracic and mediastinal disorders      |                  |  |  |
| Painful respiration                                  |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Respiratory tract inflammation                  |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Psychiatric disorders                           |                  |  |  |
| Borderline personality disorder                 |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Depression suicidal                             |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Mental fatigue                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Panic attack                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Investigations                                  |                  |  |  |
| CD4/CD8 ratio decreased                         |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Electrocardiogram QT prolonged                  |                  |  |  |
| subjects affected / exposed                     | 4 / 6998 (0.06%) |  |  |
| occurrences causally related to treatment / all | 4 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gamma-glutamyltransferase                       |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| increased                                       |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Heart rate decreased                            |                  |  |  |
| subjects affected / exposed                     | 4 / 6998 (0.06%) |  |  |
| occurrences causally related to treatment / all | 3 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Injury, poisoning and procedural complications  |                  |  |  |
| Subdural haematoma                              |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Tendon rupture                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Upper limb fracture                             |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cardiac disorders                               |                  |  |  |
| Angina pectoris                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Arrhythmia                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Atrial fibrillation                             |                  |  |  |
| subjects affected / exposed                     | 3 / 6998 (0.04%) |  |  |
| occurrences causally related to treatment / all | 1 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |

|                                                                     |                   |  |  |
|---------------------------------------------------------------------|-------------------|--|--|
| Atrioventricular block complete<br>subjects affected / exposed      | 1 / 6998 (0.01%)  |  |  |
| occurrences causally related to<br>treatment / all                  | 1 / 1             |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0             |  |  |
| Atrioventricular block second degree<br>subjects affected / exposed | 49 / 6998 (0.70%) |  |  |
| occurrences causally related to<br>treatment / all                  | 47 / 49           |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0             |  |  |
| Bradycardia<br>subjects affected / exposed                          | 24 / 6998 (0.34%) |  |  |
| occurrences causally related to<br>treatment / all                  | 24 / 24           |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0             |  |  |
| Coronary artery disease<br>subjects affected / exposed              | 2 / 6998 (0.03%)  |  |  |
| occurrences causally related to<br>treatment / all                  | 0 / 2             |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0             |  |  |
| Ischaemic cardiomyopathy<br>subjects affected / exposed             | 1 / 6998 (0.01%)  |  |  |
| occurrences causally related to<br>treatment / all                  | 0 / 1             |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0             |  |  |
| Myocardial infarction<br>subjects affected / exposed                | 2 / 6998 (0.03%)  |  |  |
| occurrences causally related to<br>treatment / all                  | 2 / 2             |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0             |  |  |
| Sinus bradycardia<br>subjects affected / exposed                    | 2 / 6998 (0.03%)  |  |  |
| occurrences causally related to<br>treatment / all                  | 2 / 2             |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0             |  |  |
| Supraventricular extrasystoles<br>subjects affected / exposed       | 2 / 6998 (0.03%)  |  |  |
| occurrences causally related to<br>treatment / all                  | 2 / 2             |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0             |  |  |
| Nervous system disorders                                            |                   |  |  |

|                                                 |                  |  |  |  |
|-------------------------------------------------|------------------|--|--|--|
| Ataxia                                          |                  |  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Central nervous system lesion                   |                  |  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Dizziness                                       |                  |  |  |  |
| subjects affected / exposed                     | 3 / 6998 (0.04%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 3            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Embolic cerebral infarction                     |                  |  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Epilepsy                                        |                  |  |  |  |
| subjects affected / exposed                     | 2 / 6998 (0.03%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Headache                                        |                  |  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Hypoaesthesia                                   |                  |  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Intracranial aneurysm                           |                  |  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Multiple sclerosis relapse                      |                  |  |  |  |

|                                                 |                   |  |  |
|-------------------------------------------------|-------------------|--|--|
| subjects affected / exposed                     | 26 / 6998 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 26            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Optic neuritis                                  |                   |  |  |
| subjects affected / exposed                     | 3 / 6998 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Partial seizures                                |                   |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Restless legs syndrome                          |                   |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Seizure                                         |                   |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Subdural hygroma                                |                   |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Syncope                                         |                   |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Blood and lymphatic system disorders            |                   |  |  |
| Leukocytosis                                    |                   |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Leukopenia                                      |                   |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Lymphopenia                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ear and labyrinth disorders                     |                  |  |  |
| Vertigo                                         |                  |  |  |
| subjects affected / exposed                     | 2 / 6998 (0.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Eye disorders                                   |                  |  |  |
| Macular oedema                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Visual acuity reduced                           |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastrointestinal disorders                      |                  |  |  |
| Abdominal discomfort                            |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Anal fistula                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Diarrhoea                                       |                  |  |  |
| subjects affected / exposed                     | 2 / 6998 (0.03%) |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |



|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| Dysphagia                                       |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Mouth haemorrhage                               |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Nausea                                          |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pancreatitis                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Skin and subcutaneous tissue disorders          |                  |  |  |
| Skin irritation                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal and urinary disorders                     |                  |  |  |
| Calculus urethral                               |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Musculoskeletal and connective tissue disorders |                  |  |  |
| Muscle spasms                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Myalgia                                         |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Infections and infestations</b>              |                  |  |  |
| <b>Abdominal abscess</b>                        |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Anal abscess</b>                             |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Cellulitis</b>                               |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Cystitis</b>                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Gastroenteritis</b>                          |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Herpes zoster</b>                            |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Infection</b>                                |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Oral herpes</b>                              |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pyelonephritis                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                                   | Fingolimod 0.5 mg    |  |  |
|---------------------------------------------------------------------|----------------------|--|--|
| Total subjects affected by non-serious adverse events               |                      |  |  |
| subjects affected / exposed                                         | 2179 / 6998 (31.14%) |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                      |  |  |
| Basal cell carcinoma                                                |                      |  |  |
| subjects affected / exposed                                         | 1 / 6998 (0.01%)     |  |  |
| occurrences (all)                                                   | 1                    |  |  |
| Pharyngeal neoplasm benign                                          |                      |  |  |
| subjects affected / exposed                                         | 1 / 6998 (0.01%)     |  |  |
| occurrences (all)                                                   | 1                    |  |  |
| Vascular disorders                                                  |                      |  |  |
| Blood pressure fluctuation                                          |                      |  |  |
| subjects affected / exposed                                         | 2 / 6998 (0.03%)     |  |  |
| occurrences (all)                                                   | 2                    |  |  |
| Circulatory collapse                                                |                      |  |  |
| subjects affected / exposed                                         | 1 / 6998 (0.01%)     |  |  |
| occurrences (all)                                                   | 1                    |  |  |
| Diastolic hypertension                                              |                      |  |  |
| subjects affected / exposed                                         | 1 / 6998 (0.01%)     |  |  |
| occurrences (all)                                                   | 1                    |  |  |
| Flushing                                                            |                      |  |  |
| subjects affected / exposed                                         | 4 / 6998 (0.06%)     |  |  |
| occurrences (all)                                                   | 4                    |  |  |
| Haematoma                                                           |                      |  |  |

|                                                                                                                                       |                         |  |  |
|---------------------------------------------------------------------------------------------------------------------------------------|-------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                                                                                      | 1 / 6998 (0.01%)<br>1   |  |  |
| Hot flush<br>subjects affected / exposed<br>occurrences (all)                                                                         | 3 / 6998 (0.04%)<br>3   |  |  |
| Hypertension<br>subjects affected / exposed<br>occurrences (all)                                                                      | 64 / 6998 (0.91%)<br>64 |  |  |
| Hypotension<br>subjects affected / exposed<br>occurrences (all)                                                                       | 12 / 6998 (0.17%)<br>12 |  |  |
| Pallor<br>subjects affected / exposed<br>occurrences (all)                                                                            | 1 / 6998 (0.01%)<br>1   |  |  |
| Peripheral coldness<br>subjects affected / exposed<br>occurrences (all)                                                               | 2 / 6998 (0.03%)<br>2   |  |  |
| Varicose vein<br>subjects affected / exposed<br>occurrences (all)                                                                     | 1 / 6998 (0.01%)<br>1   |  |  |
| Pregnancy, puerperium and perinatal conditions<br>Pregnancy<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 6998 (0.01%)<br>1   |  |  |
| Pregnancy of unknown location<br>subjects affected / exposed<br>occurrences (all)                                                     | 1 / 6998 (0.01%)<br>1   |  |  |
| Unintended pregnancy<br>subjects affected / exposed<br>occurrences (all)                                                              | 1 / 6998 (0.01%)<br>1   |  |  |
| General disorders and administration site conditions<br>Application site reaction<br>subjects affected / exposed<br>occurrences (all) | 1 / 6998 (0.01%)<br>1   |  |  |
| Asthenia                                                                                                                              |                         |  |  |

|                             |                    |  |  |
|-----------------------------|--------------------|--|--|
| subjects affected / exposed | 10 / 6998 (0.14%)  |  |  |
| occurrences (all)           | 10                 |  |  |
| Chest discomfort            |                    |  |  |
| subjects affected / exposed | 24 / 6998 (0.34%)  |  |  |
| occurrences (all)           | 25                 |  |  |
| Chest pain                  |                    |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)   |  |  |
| occurrences (all)           | 1                  |  |  |
| Chills                      |                    |  |  |
| subjects affected / exposed | 11 / 6998 (0.16%)  |  |  |
| occurrences (all)           | 11                 |  |  |
| Chronic fatigue syndrome    |                    |  |  |
| subjects affected / exposed | 3 / 6998 (0.04%)   |  |  |
| occurrences (all)           | 3                  |  |  |
| Discomfort                  |                    |  |  |
| subjects affected / exposed | 5 / 6998 (0.07%)   |  |  |
| occurrences (all)           | 5                  |  |  |
| Face oedema                 |                    |  |  |
| subjects affected / exposed | 2 / 6998 (0.03%)   |  |  |
| occurrences (all)           | 2                  |  |  |
| Fatigue                     |                    |  |  |
| subjects affected / exposed | 227 / 6998 (3.24%) |  |  |
| occurrences (all)           | 227                |  |  |
| Feeling abnormal            |                    |  |  |
| subjects affected / exposed | 4 / 6998 (0.06%)   |  |  |
| occurrences (all)           | 4                  |  |  |
| Feeling cold                |                    |  |  |
| subjects affected / exposed | 8 / 6998 (0.11%)   |  |  |
| occurrences (all)           | 8                  |  |  |
| Feeling drunk               |                    |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)   |  |  |
| occurrences (all)           | 1                  |  |  |
| Feeling hot                 |                    |  |  |
| subjects affected / exposed | 5 / 6998 (0.07%)   |  |  |
| occurrences (all)           | 5                  |  |  |
| Gait disturbance            |                    |  |  |

|                             |                   |  |  |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 5 / 6998 (0.07%)  |  |  |
| occurrences (all)           | 5                 |  |  |
| Inflammation                |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Influenza like illness      |                   |  |  |
| subjects affected / exposed | 19 / 6998 (0.27%) |  |  |
| occurrences (all)           | 19                |  |  |
| Infusion site inflammation  |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Infusion site necrosis      |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Local swelling              |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Malaise                     |                   |  |  |
| subjects affected / exposed | 11 / 6998 (0.16%) |  |  |
| occurrences (all)           | 11                |  |  |
| Mucosal dryness             |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Non-cardiac chest pain      |                   |  |  |
| subjects affected / exposed | 31 / 6998 (0.44%) |  |  |
| occurrences (all)           | 31                |  |  |
| Oedema peripheral           |                   |  |  |
| subjects affected / exposed | 7 / 6998 (0.10%)  |  |  |
| occurrences (all)           | 7                 |  |  |
| Pain                        |                   |  |  |
| subjects affected / exposed | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)           | 2                 |  |  |
| Peripheral swelling         |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Pyrexia                     |                   |  |  |

|                                          |                   |  |  |
|------------------------------------------|-------------------|--|--|
| subjects affected / exposed              | 17 / 6998 (0.24%) |  |  |
| occurrences (all)                        | 17                |  |  |
| Secretion discharge                      |                   |  |  |
| subjects affected / exposed              | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                        | 1                 |  |  |
| Sensation of foreign body                |                   |  |  |
| subjects affected / exposed              | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                        | 1                 |  |  |
| Sense of oppression                      |                   |  |  |
| subjects affected / exposed              | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                        | 1                 |  |  |
| Temperature intolerance                  |                   |  |  |
| subjects affected / exposed              | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)                        | 2                 |  |  |
| Thirst                                   |                   |  |  |
| subjects affected / exposed              | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)                        | 2                 |  |  |
| Immune system disorders                  |                   |  |  |
| Food allergy                             |                   |  |  |
| subjects affected / exposed              | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                        | 1                 |  |  |
| Hypersensitivity                         |                   |  |  |
| subjects affected / exposed              | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)                        | 2                 |  |  |
| Seasonal allergy                         |                   |  |  |
| subjects affected / exposed              | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                        | 1                 |  |  |
| Social circumstances                     |                   |  |  |
| Walking disability                       |                   |  |  |
| subjects affected / exposed              | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                        | 1                 |  |  |
| Reproductive system and breast disorders |                   |  |  |
| Breast discomfort                        |                   |  |  |
| subjects affected / exposed              | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)                        | 2                 |  |  |
| Breast disorder                          |                   |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                               | 1                |  |  |
| Breast pain                                     |                  |  |  |
| subjects affected / exposed                     | 2 / 6998 (0.03%) |  |  |
| occurrences (all)                               | 3                |  |  |
| Breast tenderness                               |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                               | 1                |  |  |
| Cervical dysplasia                              |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                               | 1                |  |  |
| Dysmenorrhoea                                   |                  |  |  |
| subjects affected / exposed                     | 3 / 6998 (0.04%) |  |  |
| occurrences (all)                               | 3                |  |  |
| Metrorrhagia                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                               | 1                |  |  |
| Ovulation pain                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                               | 1                |  |  |
| Priapism                                        |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                               | 1                |  |  |
| Uterine haemorrhage                             |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                               | 1                |  |  |
| Vulvovaginal burning sensation                  |                  |  |  |
| subjects affected / exposed                     | 2 / 6998 (0.03%) |  |  |
| occurrences (all)                               | 2                |  |  |
| Respiratory, thoracic and mediastinal disorders |                  |  |  |
| Allergic bronchitis                             |                  |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                               | 1                |  |  |
| Asthma                                          |                  |  |  |



|                               |                   |  |  |
|-------------------------------|-------------------|--|--|
| subjects affected / exposed   | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)             | 1                 |  |  |
| Cough                         |                   |  |  |
| subjects affected / exposed   | 20 / 6998 (0.29%) |  |  |
| occurrences (all)             | 20                |  |  |
| Dysphonia                     |                   |  |  |
| subjects affected / exposed   | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)             | 1                 |  |  |
| Dyspnoea                      |                   |  |  |
| subjects affected / exposed   | 18 / 6998 (0.26%) |  |  |
| occurrences (all)             | 18                |  |  |
| Dyspnoea exertional           |                   |  |  |
| subjects affected / exposed   | 6 / 6998 (0.09%)  |  |  |
| occurrences (all)             | 6                 |  |  |
| Epistaxis                     |                   |  |  |
| subjects affected / exposed   | 4 / 6998 (0.06%)  |  |  |
| occurrences (all)             | 4                 |  |  |
| Increased bronchial secretion |                   |  |  |
| subjects affected / exposed   | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)             | 2                 |  |  |
| Nasal congestion              |                   |  |  |
| subjects affected / exposed   | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)             | 1                 |  |  |
| Nasal oedema                  |                   |  |  |
| subjects affected / exposed   | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)             | 1                 |  |  |
| Oropharyngeal pain            |                   |  |  |
| subjects affected / exposed   | 27 / 6998 (0.39%) |  |  |
| occurrences (all)             | 27                |  |  |
| Painful respiration           |                   |  |  |
| subjects affected / exposed   | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)             | 1                 |  |  |
| Pleurisy                      |                   |  |  |
| subjects affected / exposed   | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)             | 1                 |  |  |
| Respiratory distress          |                   |  |  |

|                                         |                  |  |  |
|-----------------------------------------|------------------|--|--|
| subjects affected / exposed             | 2 / 6998 (0.03%) |  |  |
| occurrences (all)                       | 2                |  |  |
| Rhinitis allergic                       |                  |  |  |
| subjects affected / exposed             | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                       | 1                |  |  |
| Rhinorrhoea                             |                  |  |  |
| subjects affected / exposed             | 4 / 6998 (0.06%) |  |  |
| occurrences (all)                       | 4                |  |  |
| Sinus disorder                          |                  |  |  |
| subjects affected / exposed             | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                       | 1                |  |  |
| Throat irritation                       |                  |  |  |
| subjects affected / exposed             | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                       | 1                |  |  |
| Throat tightness                        |                  |  |  |
| subjects affected / exposed             | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                       | 1                |  |  |
| Psychiatric disorders                   |                  |  |  |
| Adjustment disorder                     |                  |  |  |
| subjects affected / exposed             | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                       | 1                |  |  |
| Adjustment disorder with depressed mood |                  |  |  |
| subjects affected / exposed             | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                       | 1                |  |  |
| Affective disorder                      |                  |  |  |
| subjects affected / exposed             | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                       | 1                |  |  |
| Aggression                              |                  |  |  |
| subjects affected / exposed             | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                       | 1                |  |  |
| Agitation                               |                  |  |  |
| subjects affected / exposed             | 2 / 6998 (0.03%) |  |  |
| occurrences (all)                       | 2                |  |  |
| Anxiety                                 |                  |  |  |

|                             |                   |  |  |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Depressed mood              |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Depression                  |                   |  |  |
| subjects affected / exposed | 19 / 6998 (0.27%) |  |  |
| occurrences (all)           | 19                |  |  |
| Dyssomnia                   |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Emotional disorder          |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Initial insomnia            |                   |  |  |
| subjects affected / exposed | 3 / 6998 (0.04%)  |  |  |
| occurrences (all)           | 3                 |  |  |
| Insomnia                    |                   |  |  |
| subjects affected / exposed | 12 / 6998 (0.17%) |  |  |
| occurrences (all)           | 12                |  |  |
| Irritability                |                   |  |  |
| subjects affected / exposed | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)           | 2                 |  |  |
| Laziness                    |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Listless                    |                   |  |  |
| subjects affected / exposed | 4 / 6998 (0.06%)  |  |  |
| occurrences (all)           | 4                 |  |  |
| Mental disorder             |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Mental fatigue              |                   |  |  |
| subjects affected / exposed | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)           | 2                 |  |  |
| Middle insomnia             |                   |  |  |

|                                |                   |  |  |
|--------------------------------|-------------------|--|--|
| subjects affected / exposed    | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)              | 1                 |  |  |
| Mood altered                   |                   |  |  |
| subjects affected / exposed    | 3 / 6998 (0.04%)  |  |  |
| occurrences (all)              | 3                 |  |  |
| Mood swings                    |                   |  |  |
| subjects affected / exposed    | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)              | 2                 |  |  |
| Nervousness                    |                   |  |  |
| subjects affected / exposed    | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)              | 1                 |  |  |
| Nightmare                      |                   |  |  |
| subjects affected / exposed    | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)              | 1                 |  |  |
| Panic attack                   |                   |  |  |
| subjects affected / exposed    | 7 / 6998 (0.10%)  |  |  |
| occurrences (all)              | 7                 |  |  |
| Persistent depressive disorder |                   |  |  |
| subjects affected / exposed    | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)              | 1                 |  |  |
| Restlessness                   |                   |  |  |
| subjects affected / exposed    | 8 / 6998 (0.11%)  |  |  |
| occurrences (all)              | 8                 |  |  |
| Sleep disorder                 |                   |  |  |
| subjects affected / exposed    | 18 / 6998 (0.26%) |  |  |
| occurrences (all)              | 18                |  |  |
| Product issues                 |                   |  |  |
| Device defective               |                   |  |  |
| subjects affected / exposed    | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)              | 1                 |  |  |
| Hepatobiliary disorders        |                   |  |  |
| Hepatic steatosis              |                   |  |  |
| subjects affected / exposed    | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)              | 1                 |  |  |
| Hyperbilirubinaemia            |                   |  |  |

|                                      |                   |  |  |
|--------------------------------------|-------------------|--|--|
| subjects affected / exposed          | 5 / 6998 (0.07%)  |  |  |
| occurrences (all)                    | 5                 |  |  |
| Liver disorder                       |                   |  |  |
| subjects affected / exposed          | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                    | 1                 |  |  |
| Investigations                       |                   |  |  |
| Alanine aminotransferase increased   |                   |  |  |
| subjects affected / exposed          | 21 / 6998 (0.30%) |  |  |
| occurrences (all)                    | 21                |  |  |
| Aspartate aminotransferase increased |                   |  |  |
| subjects affected / exposed          | 3 / 6998 (0.04%)  |  |  |
| occurrences (all)                    | 3                 |  |  |
| Basophil count increased             |                   |  |  |
| subjects affected / exposed          | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                    | 1                 |  |  |
| Blood alkaline phosphatase increased |                   |  |  |
| subjects affected / exposed          | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                    | 1                 |  |  |
| Blood bilirubin increased            |                   |  |  |
| subjects affected / exposed          | 11 / 6998 (0.16%) |  |  |
| occurrences (all)                    | 11                |  |  |
| Blood chloride decreased             |                   |  |  |
| subjects affected / exposed          | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                    | 1                 |  |  |
| Blood creatinine increased           |                   |  |  |
| subjects affected / exposed          | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)                    | 2                 |  |  |
| Blood glucose decreased              |                   |  |  |
| subjects affected / exposed          | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)                    | 2                 |  |  |
| Blood glucose increased              |                   |  |  |
| subjects affected / exposed          | 9 / 6998 (0.13%)  |  |  |
| occurrences (all)                    | 10                |  |  |
| Blood pressure decreased             |                   |  |  |

|                                         |                   |  |  |
|-----------------------------------------|-------------------|--|--|
| subjects affected / exposed             | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                       | 1                 |  |  |
| Blood pressure diastolic decreased      |                   |  |  |
| subjects affected / exposed             | 3 / 6998 (0.04%)  |  |  |
| occurrences (all)                       | 3                 |  |  |
| Blood pressure diastolic increased      |                   |  |  |
| subjects affected / exposed             | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)                       | 2                 |  |  |
| Blood pressure increased                |                   |  |  |
| subjects affected / exposed             | 10 / 6998 (0.14%) |  |  |
| occurrences (all)                       | 10                |  |  |
| Blood pressure systolic increased       |                   |  |  |
| subjects affected / exposed             | 3 / 6998 (0.04%)  |  |  |
| occurrences (all)                       | 3                 |  |  |
| Blood urea increased                    |                   |  |  |
| subjects affected / exposed             | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                       | 1                 |  |  |
| Body temperature increased              |                   |  |  |
| subjects affected / exposed             | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                       | 1                 |  |  |
| Electrocardiogram P wave abnormal       |                   |  |  |
| subjects affected / exposed             | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                       | 1                 |  |  |
| Electrocardiogram QRS complex prolonged |                   |  |  |
| subjects affected / exposed             | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                       | 1                 |  |  |
| Electrocardiogram QT prolonged          |                   |  |  |
| subjects affected / exposed             | 9 / 6998 (0.13%)  |  |  |
| occurrences (all)                       | 9                 |  |  |
| Electrocardiogram ST segment abnormal   |                   |  |  |
| subjects affected / exposed             | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                       | 1                 |  |  |
| Electrocardiogram ST segment depression |                   |  |  |

|                                     |                   |  |  |
|-------------------------------------|-------------------|--|--|
| subjects affected / exposed         | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)                   | 2                 |  |  |
| Electrocardiogram T wave inversion  |                   |  |  |
| subjects affected / exposed         | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                   | 1                 |  |  |
| Electrocardiogram abnormal          |                   |  |  |
| subjects affected / exposed         | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                   | 1                 |  |  |
| Eosinophil count decreased          |                   |  |  |
| subjects affected / exposed         | 13 / 6998 (0.19%) |  |  |
| occurrences (all)                   | 13                |  |  |
| Eosinophil count increased          |                   |  |  |
| subjects affected / exposed         | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                   | 1                 |  |  |
| Gamma-glutamyltransferase increased |                   |  |  |
| subjects affected / exposed         | 8 / 6998 (0.11%)  |  |  |
| occurrences (all)                   | 9                 |  |  |
| Haematocrit decreased               |                   |  |  |
| subjects affected / exposed         | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                   | 1                 |  |  |
| Haematocrit increased               |                   |  |  |
| subjects affected / exposed         | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                   | 1                 |  |  |
| Haemoglobin decreased               |                   |  |  |
| subjects affected / exposed         | 3 / 6998 (0.04%)  |  |  |
| occurrences (all)                   | 3                 |  |  |
| Haemoglobin increased               |                   |  |  |
| subjects affected / exposed         | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                   | 1                 |  |  |
| Heart rate abnormal                 |                   |  |  |
| subjects affected / exposed         | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                   | 1                 |  |  |
| Heart rate decreased                |                   |  |  |
| subjects affected / exposed         | 13 / 6998 (0.19%) |  |  |
| occurrences (all)                   | 13                |  |  |

|                                                                                   |                         |  |  |
|-----------------------------------------------------------------------------------|-------------------------|--|--|
| Heart rate increased<br>subjects affected / exposed<br>occurrences (all)          | 7 / 6998 (0.10%)<br>7   |  |  |
| Hepatic enzyme increased<br>subjects affected / exposed<br>occurrences (all)      | 14 / 6998 (0.20%)<br>14 |  |  |
| Liver function test increased<br>subjects affected / exposed<br>occurrences (all) | 3 / 6998 (0.04%)<br>3   |  |  |
| Lymphocyte count abnormal<br>subjects affected / exposed<br>occurrences (all)     | 2 / 6998 (0.03%)<br>2   |  |  |
| Lymphocyte count decreased<br>subjects affected / exposed<br>occurrences (all)    | 36 / 6998 (0.51%)<br>36 |  |  |
| Lymphocyte count increased<br>subjects affected / exposed<br>occurrences (all)    | 1 / 6998 (0.01%)<br>1   |  |  |
| Monocyte count decreased<br>subjects affected / exposed<br>occurrences (all)      | 3 / 6998 (0.04%)<br>3   |  |  |
| Monocyte count increased<br>subjects affected / exposed<br>occurrences (all)      | 2 / 6998 (0.03%)<br>2   |  |  |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)    | 6 / 6998 (0.09%)<br>6   |  |  |
| Neutrophil count increased<br>subjects affected / exposed<br>occurrences (all)    | 7 / 6998 (0.10%)<br>7   |  |  |
| Platelet aggregation<br>subjects affected / exposed<br>occurrences (all)          | 1 / 6998 (0.01%)<br>1   |  |  |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)      | 1 / 6998 (0.01%)<br>1   |  |  |



|                                                |                   |  |  |
|------------------------------------------------|-------------------|--|--|
| Pulse abnormal                                 |                   |  |  |
| subjects affected / exposed                    | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                              | 1                 |  |  |
| Red blood cell count decreased                 |                   |  |  |
| subjects affected / exposed                    | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                              | 1                 |  |  |
| Transaminases increased                        |                   |  |  |
| subjects affected / exposed                    | 3 / 6998 (0.04%)  |  |  |
| occurrences (all)                              | 3                 |  |  |
| Weight decreased                               |                   |  |  |
| subjects affected / exposed                    | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)                              | 2                 |  |  |
| Weight increased                               |                   |  |  |
| subjects affected / exposed                    | 3 / 6998 (0.04%)  |  |  |
| occurrences (all)                              | 3                 |  |  |
| White blood cell count decreased               |                   |  |  |
| subjects affected / exposed                    | 18 / 6998 (0.26%) |  |  |
| occurrences (all)                              | 18                |  |  |
| White blood cell count increased               |                   |  |  |
| subjects affected / exposed                    | 5 / 6998 (0.07%)  |  |  |
| occurrences (all)                              | 5                 |  |  |
| White blood cells urine                        |                   |  |  |
| subjects affected / exposed                    | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                              | 1                 |  |  |
| Injury, poisoning and procedural complications |                   |  |  |
| Animal bite                                    |                   |  |  |
| subjects affected / exposed                    | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                              | 1                 |  |  |
| Animal scratch                                 |                   |  |  |
| subjects affected / exposed                    | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                              | 1                 |  |  |
| Chest injury                                   |                   |  |  |
| subjects affected / exposed                    | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                              | 1                 |  |  |
| Fall                                           |                   |  |  |

|                                                                                                                     |                         |  |  |
|---------------------------------------------------------------------------------------------------------------------|-------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                                                                    | 6 / 6998 (0.09%)<br>6   |  |  |
| Foot fracture<br>subjects affected / exposed<br>occurrences (all)                                                   | 1 / 6998 (0.01%)<br>1   |  |  |
| Laceration<br>subjects affected / exposed<br>occurrences (all)                                                      | 1 / 6998 (0.01%)<br>1   |  |  |
| Ligament sprain<br>subjects affected / exposed<br>occurrences (all)                                                 | 2 / 6998 (0.03%)<br>2   |  |  |
| Limb injury<br>subjects affected / exposed<br>occurrences (all)                                                     | 1 / 6998 (0.01%)<br>1   |  |  |
| Meniscus injury<br>subjects affected / exposed<br>occurrences (all)                                                 | 1 / 6998 (0.01%)<br>1   |  |  |
| Post procedural complication<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 6998 (0.01%)<br>1   |  |  |
| Skin abrasion<br>subjects affected / exposed<br>occurrences (all)                                                   | 1 / 6998 (0.01%)<br>1   |  |  |
| Thermal burn<br>subjects affected / exposed<br>occurrences (all)                                                    | 2 / 6998 (0.03%)<br>2   |  |  |
| Congenital, familial and genetic disorders<br>Corneal dystrophy<br>subjects affected / exposed<br>occurrences (all) | 1 / 6998 (0.01%)<br>1   |  |  |
| Cardiac disorders<br>Angina pectoris<br>subjects affected / exposed<br>occurrences (all)                            | 11 / 6998 (0.16%)<br>11 |  |  |
| Arrhythmia                                                                                                          |                         |  |  |

|                                      |                    |  |  |
|--------------------------------------|--------------------|--|--|
| subjects affected / exposed          | 7 / 6998 (0.10%)   |  |  |
| occurrences (all)                    | 7                  |  |  |
| Atrioventricular block first degree  |                    |  |  |
| subjects affected / exposed          | 116 / 6998 (1.66%) |  |  |
| occurrences (all)                    | 117                |  |  |
| Atrioventricular block second degree |                    |  |  |
| subjects affected / exposed          | 74 / 6998 (1.06%)  |  |  |
| occurrences (all)                    | 74                 |  |  |
| Bradycardia                          |                    |  |  |
| subjects affected / exposed          | 48 / 6998 (0.69%)  |  |  |
| occurrences (all)                    | 48                 |  |  |
| Bundle branch block right            |                    |  |  |
| subjects affected / exposed          | 1 / 6998 (0.01%)   |  |  |
| occurrences (all)                    | 1                  |  |  |
| Cardiac discomfort                   |                    |  |  |
| subjects affected / exposed          | 2 / 6998 (0.03%)   |  |  |
| occurrences (all)                    | 2                  |  |  |
| Cardiovascular disorder              |                    |  |  |
| subjects affected / exposed          | 3 / 6998 (0.04%)   |  |  |
| occurrences (all)                    | 3                  |  |  |
| Coronary artery stenosis             |                    |  |  |
| subjects affected / exposed          | 1 / 6998 (0.01%)   |  |  |
| occurrences (all)                    | 1                  |  |  |
| Extrasystoles                        |                    |  |  |
| subjects affected / exposed          | 4 / 6998 (0.06%)   |  |  |
| occurrences (all)                    | 4                  |  |  |
| Palpitations                         |                    |  |  |
| subjects affected / exposed          | 26 / 6998 (0.37%)  |  |  |
| occurrences (all)                    | 26                 |  |  |
| Pericardial effusion                 |                    |  |  |
| subjects affected / exposed          | 1 / 6998 (0.01%)   |  |  |
| occurrences (all)                    | 1                  |  |  |
| Sinus arrhythmia                     |                    |  |  |
| subjects affected / exposed          | 3 / 6998 (0.04%)   |  |  |
| occurrences (all)                    | 3                  |  |  |
| Sinus bradycardia                    |                    |  |  |

|                                |                   |  |  |
|--------------------------------|-------------------|--|--|
| subjects affected / exposed    | 8 / 6998 (0.11%)  |  |  |
| occurrences (all)              | 8                 |  |  |
| Sinus tachycardia              |                   |  |  |
| subjects affected / exposed    | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)              | 2                 |  |  |
| Supraventricular extrasystoles |                   |  |  |
| subjects affected / exposed    | 10 / 6998 (0.14%) |  |  |
| occurrences (all)              | 10                |  |  |
| Tachycardia                    |                   |  |  |
| subjects affected / exposed    | 6 / 6998 (0.09%)  |  |  |
| occurrences (all)              | 6                 |  |  |
| Ventricular extrasystoles      |                   |  |  |
| subjects affected / exposed    | 4 / 6998 (0.06%)  |  |  |
| occurrences (all)              | 4                 |  |  |
| Ventricular pre-excitation     |                   |  |  |
| subjects affected / exposed    | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)              | 1                 |  |  |
| Ventricular tachycardia        |                   |  |  |
| subjects affected / exposed    | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)              | 1                 |  |  |
| Nervous system disorders       |                   |  |  |
| Aphasia                        |                   |  |  |
| subjects affected / exposed    | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)              | 1                 |  |  |
| Ataxia                         |                   |  |  |
| subjects affected / exposed    | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)              | 1                 |  |  |
| Balance disorder               |                   |  |  |
| subjects affected / exposed    | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)              | 2                 |  |  |
| Carpal tunnel syndrome         |                   |  |  |
| subjects affected / exposed    | 3 / 6998 (0.04%)  |  |  |
| occurrences (all)              | 3                 |  |  |
| Disturbance in attention       |                   |  |  |
| subjects affected / exposed    | 4 / 6998 (0.06%)  |  |  |
| occurrences (all)              | 4                 |  |  |

|                             |                    |  |  |
|-----------------------------|--------------------|--|--|
| Dizziness                   |                    |  |  |
| subjects affected / exposed | 126 / 6998 (1.80%) |  |  |
| occurrences (all)           | 126                |  |  |
| Dizziness exertional        |                    |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)   |  |  |
| occurrences (all)           | 1                  |  |  |
| Dizziness postural          |                    |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)   |  |  |
| occurrences (all)           | 1                  |  |  |
| Dysaesthesia                |                    |  |  |
| subjects affected / exposed | 5 / 6998 (0.07%)   |  |  |
| occurrences (all)           | 5                  |  |  |
| Dysgeusia                   |                    |  |  |
| subjects affected / exposed | 21 / 6998 (0.30%)  |  |  |
| occurrences (all)           | 21                 |  |  |
| Epilepsy                    |                    |  |  |
| subjects affected / exposed | 2 / 6998 (0.03%)   |  |  |
| occurrences (all)           | 2                  |  |  |
| Facial spasm                |                    |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)   |  |  |
| occurrences (all)           | 1                  |  |  |
| Head discomfort             |                    |  |  |
| subjects affected / exposed | 6 / 6998 (0.09%)   |  |  |
| occurrences (all)           | 6                  |  |  |
| Headache                    |                    |  |  |
| subjects affected / exposed | 316 / 6998 (4.52%) |  |  |
| occurrences (all)           | 325                |  |  |
| Hemiparesis                 |                    |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)   |  |  |
| occurrences (all)           | 1                  |  |  |
| Hyperaesthesia              |                    |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)   |  |  |
| occurrences (all)           | 1                  |  |  |
| Hypertonia                  |                    |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)   |  |  |
| occurrences (all)           | 1                  |  |  |

|                             |                   |  |  |
|-----------------------------|-------------------|--|--|
| Hypoaesthesia               |                   |  |  |
| subjects affected / exposed | 14 / 6998 (0.20%) |  |  |
| occurrences (all)           | 14                |  |  |
| Lhermitte's sign            |                   |  |  |
| subjects affected / exposed | 3 / 6998 (0.04%)  |  |  |
| occurrences (all)           | 3                 |  |  |
| Migraine                    |                   |  |  |
| subjects affected / exposed | 17 / 6998 (0.24%) |  |  |
| occurrences (all)           | 18                |  |  |
| Migraine with aura          |                   |  |  |
| subjects affected / exposed | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)           | 2                 |  |  |
| Monoparesis                 |                   |  |  |
| subjects affected / exposed | 3 / 6998 (0.04%)  |  |  |
| occurrences (all)           | 3                 |  |  |
| Multiple sclerosis          |                   |  |  |
| subjects affected / exposed | 3 / 6998 (0.04%)  |  |  |
| occurrences (all)           | 3                 |  |  |
| Multiple sclerosis relapse  |                   |  |  |
| subjects affected / exposed | 70 / 6998 (1.00%) |  |  |
| occurrences (all)           | 70                |  |  |
| Muscle spasticity           |                   |  |  |
| subjects affected / exposed | 6 / 6998 (0.09%)  |  |  |
| occurrences (all)           | 6                 |  |  |
| Neuralgia                   |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Neuropathy peripheral       |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Optic neuritis              |                   |  |  |
| subjects affected / exposed | 4 / 6998 (0.06%)  |  |  |
| occurrences (all)           | 4                 |  |  |
| Orthostatic intolerance     |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |

|                             |                   |  |  |
|-----------------------------|-------------------|--|--|
| Paraesthesia                |                   |  |  |
| subjects affected / exposed | 29 / 6998 (0.41%) |  |  |
| occurrences (all)           | 29                |  |  |
| Peroneal nerve palsy        |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Presyncope                  |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Psychogenic pseudosyncope   |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Radial nerve compression    |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Restless legs syndrome      |                   |  |  |
| subjects affected / exposed | 3 / 6998 (0.04%)  |  |  |
| occurrences (all)           | 3                 |  |  |
| Sciatica                    |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Sensory disturbance         |                   |  |  |
| subjects affected / exposed | 7 / 6998 (0.10%)  |  |  |
| occurrences (all)           | 7                 |  |  |
| Somnolence                  |                   |  |  |
| subjects affected / exposed | 5 / 6998 (0.07%)  |  |  |
| occurrences (all)           | 5                 |  |  |
| Syncope                     |                   |  |  |
| subjects affected / exposed | 5 / 6998 (0.07%)  |  |  |
| occurrences (all)           | 5                 |  |  |
| Tension headache            |                   |  |  |
| subjects affected / exposed | 3 / 6998 (0.04%)  |  |  |
| occurrences (all)           | 3                 |  |  |
| Tremor                      |                   |  |  |
| subjects affected / exposed | 9 / 6998 (0.13%)  |  |  |
| occurrences (all)           | 9                 |  |  |

|                                                                          |                           |  |  |
|--------------------------------------------------------------------------|---------------------------|--|--|
| Trigeminal neuralgia<br>subjects affected / exposed<br>occurrences (all) | 3 / 6998 (0.04%)<br>3     |  |  |
| Visual field defect<br>subjects affected / exposed<br>occurrences (all)  | 1 / 6998 (0.01%)<br>1     |  |  |
| Blood and lymphatic system disorders                                     |                           |  |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)              | 4 / 6998 (0.06%)<br>4     |  |  |
| Eosinopenia<br>subjects affected / exposed<br>occurrences (all)          | 7 / 6998 (0.10%)<br>7     |  |  |
| Eosinophilia<br>subjects affected / exposed<br>occurrences (all)         | 12 / 6998 (0.17%)<br>12   |  |  |
| Granulocytosis<br>subjects affected / exposed<br>occurrences (all)       | 1 / 6998 (0.01%)<br>1     |  |  |
| Haemoglobinaemia<br>subjects affected / exposed<br>occurrences (all)     | 1 / 6998 (0.01%)<br>1     |  |  |
| Leukocytosis<br>subjects affected / exposed<br>occurrences (all)         | 11 / 6998 (0.16%)<br>11   |  |  |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)           | 68 / 6998 (0.97%)<br>68   |  |  |
| Lymphadenopathy<br>subjects affected / exposed<br>occurrences (all)      | 5 / 6998 (0.07%)<br>5     |  |  |
| Lymphopenia<br>subjects affected / exposed<br>occurrences (all)          | 119 / 6998 (1.70%)<br>119 |  |  |
| Microcytic anaemia                                                       |                           |  |  |



|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 6998 (0.01%) |  |  |
| occurrences (all)           | 1                |  |  |
| Monocytopenia               |                  |  |  |
| subjects affected / exposed | 4 / 6998 (0.06%) |  |  |
| occurrences (all)           | 4                |  |  |
| Monocytosis                 |                  |  |  |
| subjects affected / exposed | 2 / 6998 (0.03%) |  |  |
| occurrences (all)           | 2                |  |  |
| Neutropenia                 |                  |  |  |
| subjects affected / exposed | 9 / 6998 (0.13%) |  |  |
| occurrences (all)           | 9                |  |  |
| Neutrophilia                |                  |  |  |
| subjects affected / exposed | 5 / 6998 (0.07%) |  |  |
| occurrences (all)           | 5                |  |  |
| Pancytopenia                |                  |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%) |  |  |
| occurrences (all)           | 1                |  |  |
| Thrombocytopenia            |                  |  |  |
| subjects affected / exposed | 7 / 6998 (0.10%) |  |  |
| occurrences (all)           | 7                |  |  |
| Ear and labyrinth disorders |                  |  |  |
| Deafness                    |                  |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%) |  |  |
| occurrences (all)           | 1                |  |  |
| Ear discomfort              |                  |  |  |
| subjects affected / exposed | 3 / 6998 (0.04%) |  |  |
| occurrences (all)           | 3                |  |  |
| Ear pain                    |                  |  |  |
| subjects affected / exposed | 3 / 6998 (0.04%) |  |  |
| occurrences (all)           | 3                |  |  |
| External ear inflammation   |                  |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%) |  |  |
| occurrences (all)           | 1                |  |  |
| Sudden hearing loss         |                  |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%) |  |  |
| occurrences (all)           | 1                |  |  |

|                                |                   |  |  |
|--------------------------------|-------------------|--|--|
| Tinnitus                       |                   |  |  |
| subjects affected / exposed    | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)              | 2                 |  |  |
| Vertigo                        |                   |  |  |
| subjects affected / exposed    | 68 / 6998 (0.97%) |  |  |
| occurrences (all)              | 69                |  |  |
| Vertigo positional             |                   |  |  |
| subjects affected / exposed    | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)              | 1                 |  |  |
| Eye disorders                  |                   |  |  |
| Amblyopia                      |                   |  |  |
| subjects affected / exposed    | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)              | 2                 |  |  |
| Blepharospasm                  |                   |  |  |
| subjects affected / exposed    | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)              | 1                 |  |  |
| Cataract                       |                   |  |  |
| subjects affected / exposed    | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)              | 1                 |  |  |
| Diplopia                       |                   |  |  |
| subjects affected / exposed    | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)              | 2                 |  |  |
| Eye irritation                 |                   |  |  |
| subjects affected / exposed    | 3 / 6998 (0.04%)  |  |  |
| occurrences (all)              | 3                 |  |  |
| Eye pain                       |                   |  |  |
| subjects affected / exposed    | 11 / 6998 (0.16%) |  |  |
| occurrences (all)              | 12                |  |  |
| Eye swelling                   |                   |  |  |
| subjects affected / exposed    | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)              | 1                 |  |  |
| Eyelid oedema                  |                   |  |  |
| subjects affected / exposed    | 3 / 6998 (0.04%)  |  |  |
| occurrences (all)              | 3                 |  |  |
| Foreign body sensation in eyes |                   |  |  |

|                             |                   |  |  |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Iridocyclitis               |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Macular oedema              |                   |  |  |
| subjects affected / exposed | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)           | 2                 |  |  |
| Ocular discomfort           |                   |  |  |
| subjects affected / exposed | 6 / 6998 (0.09%)  |  |  |
| occurrences (all)           | 6                 |  |  |
| Photopsia                   |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Retinal vein thrombosis     |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Vision blurred              |                   |  |  |
| subjects affected / exposed | 20 / 6998 (0.29%) |  |  |
| occurrences (all)           | 20                |  |  |
| Visual acuity reduced       |                   |  |  |
| subjects affected / exposed | 3 / 6998 (0.04%)  |  |  |
| occurrences (all)           | 3                 |  |  |
| Visual impairment           |                   |  |  |
| subjects affected / exposed | 6 / 6998 (0.09%)  |  |  |
| occurrences (all)           | 6                 |  |  |
| Gastrointestinal disorders  |                   |  |  |
| Abdominal discomfort        |                   |  |  |
| subjects affected / exposed | 9 / 6998 (0.13%)  |  |  |
| occurrences (all)           | 9                 |  |  |
| Abdominal distension        |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Abdominal pain              |                   |  |  |
| subjects affected / exposed | 9 / 6998 (0.13%)  |  |  |
| occurrences (all)           | 10                |  |  |

|                                                                                 |                         |  |  |
|---------------------------------------------------------------------------------|-------------------------|--|--|
| Abdominal pain lower<br>subjects affected / exposed<br>occurrences (all)        | 2 / 6998 (0.03%)<br>2   |  |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)        | 53 / 6998 (0.76%)<br>53 |  |  |
| Anal incontinence<br>subjects affected / exposed<br>occurrences (all)           | 2 / 6998 (0.03%)<br>2   |  |  |
| Aphthous ulcer<br>subjects affected / exposed<br>occurrences (all)              | 1 / 6998 (0.01%)<br>1   |  |  |
| Bowel movement irregularity<br>subjects affected / exposed<br>occurrences (all) | 1 / 6998 (0.01%)<br>1   |  |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                | 13 / 6998 (0.19%)<br>13 |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                   | 96 / 6998 (1.37%)<br>96 |  |  |
| Dry mouth<br>subjects affected / exposed<br>occurrences (all)                   | 7 / 6998 (0.10%)<br>7   |  |  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)                   | 11 / 6998 (0.16%)<br>11 |  |  |
| Dysphagia<br>subjects affected / exposed<br>occurrences (all)                   | 2 / 6998 (0.03%)<br>2   |  |  |
| Enteritis<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 6998 (0.01%)<br>1   |  |  |
| Eructation<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 6998 (0.01%)<br>1   |  |  |

|                                  |                    |  |  |
|----------------------------------|--------------------|--|--|
| Faeces soft                      |                    |  |  |
| subjects affected / exposed      | 1 / 6998 (0.01%)   |  |  |
| occurrences (all)                | 1                  |  |  |
| Flatulence                       |                    |  |  |
| subjects affected / exposed      | 9 / 6998 (0.13%)   |  |  |
| occurrences (all)                | 9                  |  |  |
| Frequent bowel movements         |                    |  |  |
| subjects affected / exposed      | 1 / 6998 (0.01%)   |  |  |
| occurrences (all)                | 1                  |  |  |
| Gastric disorder                 |                    |  |  |
| subjects affected / exposed      | 2 / 6998 (0.03%)   |  |  |
| occurrences (all)                | 2                  |  |  |
| Gastritis                        |                    |  |  |
| subjects affected / exposed      | 2 / 6998 (0.03%)   |  |  |
| occurrences (all)                | 2                  |  |  |
| Gastrointestinal disorder        |                    |  |  |
| subjects affected / exposed      | 2 / 6998 (0.03%)   |  |  |
| occurrences (all)                | 2                  |  |  |
| Gastrointestinal erosion         |                    |  |  |
| subjects affected / exposed      | 1 / 6998 (0.01%)   |  |  |
| occurrences (all)                | 1                  |  |  |
| Gastrooesophageal reflux disease |                    |  |  |
| subjects affected / exposed      | 2 / 6998 (0.03%)   |  |  |
| occurrences (all)                | 2                  |  |  |
| Haemorrhoids                     |                    |  |  |
| subjects affected / exposed      | 1 / 6998 (0.01%)   |  |  |
| occurrences (all)                | 1                  |  |  |
| Nausea                           |                    |  |  |
| subjects affected / exposed      | 143 / 6998 (2.04%) |  |  |
| occurrences (all)                | 143                |  |  |
| Odynophagia                      |                    |  |  |
| subjects affected / exposed      | 1 / 6998 (0.01%)   |  |  |
| occurrences (all)                | 1                  |  |  |
| Oral dysaesthesia                |                    |  |  |
| subjects affected / exposed      | 1 / 6998 (0.01%)   |  |  |
| occurrences (all)                | 1                  |  |  |

|                                        |                   |  |  |
|----------------------------------------|-------------------|--|--|
| Oral pain                              |                   |  |  |
| subjects affected / exposed            | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                      | 1                 |  |  |
| Oral pruritus                          |                   |  |  |
| subjects affected / exposed            | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                      | 1                 |  |  |
| Paraesthesia oral                      |                   |  |  |
| subjects affected / exposed            | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)                      | 2                 |  |  |
| Tongue blistering                      |                   |  |  |
| subjects affected / exposed            | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                      | 1                 |  |  |
| Tooth disorder                         |                   |  |  |
| subjects affected / exposed            | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                      | 1                 |  |  |
| Toothache                              |                   |  |  |
| subjects affected / exposed            | 6 / 6998 (0.09%)  |  |  |
| occurrences (all)                      | 6                 |  |  |
| Vomiting                               |                   |  |  |
| subjects affected / exposed            | 13 / 6998 (0.19%) |  |  |
| occurrences (all)                      | 13                |  |  |
| Skin and subcutaneous tissue disorders |                   |  |  |
| Acne                                   |                   |  |  |
| subjects affected / exposed            | 8 / 6998 (0.11%)  |  |  |
| occurrences (all)                      | 8                 |  |  |
| Alopecia                               |                   |  |  |
| subjects affected / exposed            | 15 / 6998 (0.21%) |  |  |
| occurrences (all)                      | 15                |  |  |
| Blister                                |                   |  |  |
| subjects affected / exposed            | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                      | 1                 |  |  |
| Dermatitis                             |                   |  |  |
| subjects affected / exposed            | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)                      | 2                 |  |  |
| Dermatitis allergic                    |                   |  |  |

|                             |                   |  |  |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 4 / 6998 (0.06%)  |  |  |
| occurrences (all)           | 4                 |  |  |
| Dermatitis contact          |                   |  |  |
| subjects affected / exposed | 3 / 6998 (0.04%)  |  |  |
| occurrences (all)           | 3                 |  |  |
| Dermatitis exfoliative      |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Dermatosis                  |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Drug eruption               |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Dry skin                    |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Dyshidrotic eczema          |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Eczema                      |                   |  |  |
| subjects affected / exposed | 3 / 6998 (0.04%)  |  |  |
| occurrences (all)           | 3                 |  |  |
| Erythema                    |                   |  |  |
| subjects affected / exposed | 4 / 6998 (0.06%)  |  |  |
| occurrences (all)           | 4                 |  |  |
| Hand dermatitis             |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Hyperhidrosis               |                   |  |  |
| subjects affected / exposed | 14 / 6998 (0.20%) |  |  |
| occurrences (all)           | 15                |  |  |
| Night sweats                |                   |  |  |
| subjects affected / exposed | 3 / 6998 (0.04%)  |  |  |
| occurrences (all)           | 3                 |  |  |
| Photosensitivity reaction   |                   |  |  |

|                             |                   |  |  |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Pigmentation disorder       |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Pityriasis rosea            |                   |  |  |
| subjects affected / exposed | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)           | 2                 |  |  |
| Pruritus                    |                   |  |  |
| subjects affected / exposed | 24 / 6998 (0.34%) |  |  |
| occurrences (all)           | 24                |  |  |
| Pruritus generalised        |                   |  |  |
| subjects affected / exposed | 4 / 6998 (0.06%)  |  |  |
| occurrences (all)           | 4                 |  |  |
| Rash                        |                   |  |  |
| subjects affected / exposed | 15 / 6998 (0.21%) |  |  |
| occurrences (all)           | 15                |  |  |
| Rash pruritic               |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Rash vesicular              |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Rosacea                     |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Seborrhoeic dermatitis      |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Skin burning sensation      |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Skin disorder               |                   |  |  |
| subjects affected / exposed | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)           | 2                 |  |  |
| Skin exfoliation            |                   |  |  |



|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 6998 (0.01%) |  |  |
| occurrences (all)           | 1                |  |  |
| Skin irritation             |                  |  |  |
| subjects affected / exposed | 2 / 6998 (0.03%) |  |  |
| occurrences (all)           | 2                |  |  |
| Skin odour abnormal         |                  |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%) |  |  |
| occurrences (all)           | 1                |  |  |
| Skin reaction               |                  |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%) |  |  |
| occurrences (all)           | 1                |  |  |
| Swelling face               |                  |  |  |
| subjects affected / exposed | 2 / 6998 (0.03%) |  |  |
| occurrences (all)           | 2                |  |  |
| Renal and urinary disorders |                  |  |  |
| Bladder dysfunction         |                  |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%) |  |  |
| occurrences (all)           | 1                |  |  |
| Dysuria                     |                  |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%) |  |  |
| occurrences (all)           | 1                |  |  |
| Haematuria                  |                  |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%) |  |  |
| occurrences (all)           | 1                |  |  |
| Micturition urgency         |                  |  |  |
| subjects affected / exposed | 2 / 6998 (0.03%) |  |  |
| occurrences (all)           | 2                |  |  |
| Nephritis                   |                  |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%) |  |  |
| occurrences (all)           | 1                |  |  |
| Neurogenic bladder          |                  |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%) |  |  |
| occurrences (all)           | 1                |  |  |
| Nocturia                    |                  |  |  |
| subjects affected / exposed | 2 / 6998 (0.03%) |  |  |
| occurrences (all)           | 2                |  |  |

|                                                 |                   |  |  |
|-------------------------------------------------|-------------------|--|--|
| Pollakiuria                                     |                   |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                               | 1                 |  |  |
| Renal pain                                      |                   |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                               | 1                 |  |  |
| Urge incontinence                               |                   |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                               | 1                 |  |  |
| Musculoskeletal and connective tissue disorders |                   |  |  |
| Arthralgia                                      |                   |  |  |
| subjects affected / exposed                     | 16 / 6998 (0.23%) |  |  |
| occurrences (all)                               | 17                |  |  |
| Arthritis                                       |                   |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                               | 1                 |  |  |
| Back pain                                       |                   |  |  |
| subjects affected / exposed                     | 46 / 6998 (0.66%) |  |  |
| occurrences (all)                               | 46                |  |  |
| Bone pain                                       |                   |  |  |
| subjects affected / exposed                     | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)                               | 2                 |  |  |
| Bursitis                                        |                   |  |  |
| subjects affected / exposed                     | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)                               | 2                 |  |  |
| Coccydynia                                      |                   |  |  |
| subjects affected / exposed                     | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                               | 1                 |  |  |
| Flank pain                                      |                   |  |  |
| subjects affected / exposed                     | 3 / 6998 (0.04%)  |  |  |
| occurrences (all)                               | 3                 |  |  |
| Groin pain                                      |                   |  |  |
| subjects affected / exposed                     | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)                               | 2                 |  |  |
| Intervertebral disc protrusion                  |                   |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 6998 (0.01%) |  |  |
| occurrences (all)           | 1                |  |  |
| Joint stiffness             |                  |  |  |
| subjects affected / exposed | 2 / 6998 (0.03%) |  |  |
| occurrences (all)           | 2                |  |  |
| Limb discomfort             |                  |  |  |
| subjects affected / exposed | 6 / 6998 (0.09%) |  |  |
| occurrences (all)           | 6                |  |  |
| Mobility decreased          |                  |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%) |  |  |
| occurrences (all)           | 1                |  |  |
| Muscle fatigue              |                  |  |  |
| subjects affected / exposed | 2 / 6998 (0.03%) |  |  |
| occurrences (all)           | 2                |  |  |
| Muscle rigidity             |                  |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%) |  |  |
| occurrences (all)           | 1                |  |  |
| Muscle spasms               |                  |  |  |
| subjects affected / exposed | 3 / 6998 (0.04%) |  |  |
| occurrences (all)           | 3                |  |  |
| Muscle tightness            |                  |  |  |
| subjects affected / exposed | 3 / 6998 (0.04%) |  |  |
| occurrences (all)           | 3                |  |  |
| Muscle twitching            |                  |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%) |  |  |
| occurrences (all)           | 1                |  |  |
| Muscular weakness           |                  |  |  |
| subjects affected / exposed | 8 / 6998 (0.11%) |  |  |
| occurrences (all)           | 8                |  |  |
| Musculoskeletal chest pain  |                  |  |  |
| subjects affected / exposed | 2 / 6998 (0.03%) |  |  |
| occurrences (all)           | 2                |  |  |
| Musculoskeletal pain        |                  |  |  |
| subjects affected / exposed | 3 / 6998 (0.04%) |  |  |
| occurrences (all)           | 3                |  |  |
| Musculoskeletal stiffness   |                  |  |  |

|                             |                   |  |  |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)           | 2                 |  |  |
| Myalgia                     |                   |  |  |
| subjects affected / exposed | 16 / 6998 (0.23%) |  |  |
| occurrences (all)           | 17                |  |  |
| Myofascial pain syndrome    |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Neck pain                   |                   |  |  |
| subjects affected / exposed | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)           | 2                 |  |  |
| Pain in extremity           |                   |  |  |
| subjects affected / exposed | 19 / 6998 (0.27%) |  |  |
| occurrences (all)           | 19                |  |  |
| Spinal disorder             |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Infections and infestations |                   |  |  |
| Anal abscess                |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Anorectal infection         |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Bacterial infection         |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Bronchitis                  |                   |  |  |
| subjects affected / exposed | 7 / 6998 (0.10%)  |  |  |
| occurrences (all)           | 7                 |  |  |
| Chronic sinusitis           |                   |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)           | 1                 |  |  |
| Conjunctivitis              |                   |  |  |
| subjects affected / exposed | 2 / 6998 (0.03%)  |  |  |
| occurrences (all)           | 2                 |  |  |

|                               |                  |  |  |
|-------------------------------|------------------|--|--|
| Cystitis                      |                  |  |  |
| subjects affected / exposed   | 6 / 6998 (0.09%) |  |  |
| occurrences (all)             | 6                |  |  |
| Dysentery                     |                  |  |  |
| subjects affected / exposed   | 2 / 6998 (0.03%) |  |  |
| occurrences (all)             | 2                |  |  |
| Erysipelas                    |                  |  |  |
| subjects affected / exposed   | 1 / 6998 (0.01%) |  |  |
| occurrences (all)             | 1                |  |  |
| Febrile infection             |                  |  |  |
| subjects affected / exposed   | 2 / 6998 (0.03%) |  |  |
| occurrences (all)             | 2                |  |  |
| Fungal infection              |                  |  |  |
| subjects affected / exposed   | 1 / 6998 (0.01%) |  |  |
| occurrences (all)             | 1                |  |  |
| Gastroenteritis               |                  |  |  |
| subjects affected / exposed   | 4 / 6998 (0.06%) |  |  |
| occurrences (all)             | 4                |  |  |
| Gastroenteritis viral         |                  |  |  |
| subjects affected / exposed   | 1 / 6998 (0.01%) |  |  |
| occurrences (all)             | 1                |  |  |
| Gastrointestinal infection    |                  |  |  |
| subjects affected / exposed   | 5 / 6998 (0.07%) |  |  |
| occurrences (all)             | 5                |  |  |
| Genital herpes                |                  |  |  |
| subjects affected / exposed   | 1 / 6998 (0.01%) |  |  |
| occurrences (all)             | 1                |  |  |
| Genitourinary tract infection |                  |  |  |
| subjects affected / exposed   | 1 / 6998 (0.01%) |  |  |
| occurrences (all)             | 1                |  |  |
| Gingivitis                    |                  |  |  |
| subjects affected / exposed   | 2 / 6998 (0.03%) |  |  |
| occurrences (all)             | 2                |  |  |
| Helminthic infection          |                  |  |  |
| subjects affected / exposed   | 1 / 6998 (0.01%) |  |  |
| occurrences (all)             | 1                |  |  |

|                             |                    |  |  |
|-----------------------------|--------------------|--|--|
| Herpes simplex              |                    |  |  |
| subjects affected / exposed | 3 / 6998 (0.04%)   |  |  |
| occurrences (all)           | 3                  |  |  |
| Herpes virus infection      |                    |  |  |
| subjects affected / exposed | 2 / 6998 (0.03%)   |  |  |
| occurrences (all)           | 2                  |  |  |
| Herpes zoster               |                    |  |  |
| subjects affected / exposed | 4 / 6998 (0.06%)   |  |  |
| occurrences (all)           | 4                  |  |  |
| Hordeolum                   |                    |  |  |
| subjects affected / exposed | 2 / 6998 (0.03%)   |  |  |
| occurrences (all)           | 2                  |  |  |
| Infected bite               |                    |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)   |  |  |
| occurrences (all)           | 1                  |  |  |
| Infection                   |                    |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)   |  |  |
| occurrences (all)           | 1                  |  |  |
| Influenza                   |                    |  |  |
| subjects affected / exposed | 23 / 6998 (0.33%)  |  |  |
| occurrences (all)           | 23                 |  |  |
| Laryngitis                  |                    |  |  |
| subjects affected / exposed | 3 / 6998 (0.04%)   |  |  |
| occurrences (all)           | 3                  |  |  |
| Mastoiditis                 |                    |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)   |  |  |
| occurrences (all)           | 1                  |  |  |
| Myelitis                    |                    |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)   |  |  |
| occurrences (all)           | 1                  |  |  |
| Nasopharyngitis             |                    |  |  |
| subjects affected / exposed | 137 / 6998 (1.96%) |  |  |
| occurrences (all)           | 137                |  |  |
| Onychomycosis               |                    |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%)   |  |  |
| occurrences (all)           | 1                  |  |  |

|                                   |                   |  |  |
|-----------------------------------|-------------------|--|--|
| Oral herpes                       |                   |  |  |
| subjects affected / exposed       | 27 / 6998 (0.39%) |  |  |
| occurrences (all)                 | 27                |  |  |
| Pharyngitis                       |                   |  |  |
| subjects affected / exposed       | 3 / 6998 (0.04%)  |  |  |
| occurrences (all)                 | 3                 |  |  |
| Pyelonephritis                    |                   |  |  |
| subjects affected / exposed       | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                 | 1                 |  |  |
| Respiratory tract infection       |                   |  |  |
| subjects affected / exposed       | 7 / 6998 (0.10%)  |  |  |
| occurrences (all)                 | 7                 |  |  |
| Rhinitis                          |                   |  |  |
| subjects affected / exposed       | 12 / 6998 (0.17%) |  |  |
| occurrences (all)                 | 12                |  |  |
| Sialoadenitis                     |                   |  |  |
| subjects affected / exposed       | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                 | 1                 |  |  |
| Sinusitis                         |                   |  |  |
| subjects affected / exposed       | 6 / 6998 (0.09%)  |  |  |
| occurrences (all)                 | 6                 |  |  |
| Tinea versicolour                 |                   |  |  |
| subjects affected / exposed       | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                 | 1                 |  |  |
| Tonsillitis                       |                   |  |  |
| subjects affected / exposed       | 5 / 6998 (0.07%)  |  |  |
| occurrences (all)                 | 5                 |  |  |
| Upper respiratory tract infection |                   |  |  |
| subjects affected / exposed       | 12 / 6998 (0.17%) |  |  |
| occurrences (all)                 | 12                |  |  |
| Urinary tract infection           |                   |  |  |
| subjects affected / exposed       | 15 / 6998 (0.21%) |  |  |
| occurrences (all)                 | 15                |  |  |
| Vaginal abscess                   |                   |  |  |
| subjects affected / exposed       | 1 / 6998 (0.01%)  |  |  |
| occurrences (all)                 | 1                 |  |  |

|                                    |                  |  |  |
|------------------------------------|------------------|--|--|
| Viral infection                    |                  |  |  |
| subjects affected / exposed        | 2 / 6998 (0.03%) |  |  |
| occurrences (all)                  | 2                |  |  |
| Viral rhinitis                     |                  |  |  |
| subjects affected / exposed        | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                  | 1                |  |  |
| Vulvovaginal candidiasis           |                  |  |  |
| subjects affected / exposed        | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                  | 1                |  |  |
| Vulvovaginal mycotic infection     |                  |  |  |
| subjects affected / exposed        | 5 / 6998 (0.07%) |  |  |
| occurrences (all)                  | 5                |  |  |
| Metabolism and nutrition disorders |                  |  |  |
| Decreased appetite                 |                  |  |  |
| subjects affected / exposed        | 9 / 6998 (0.13%) |  |  |
| occurrences (all)                  | 9                |  |  |
| Food craving                       |                  |  |  |
| subjects affected / exposed        | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                  | 1                |  |  |
| Gluten sensitivity                 |                  |  |  |
| subjects affected / exposed        | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                  | 1                |  |  |
| Hyperglycaemia                     |                  |  |  |
| subjects affected / exposed        | 4 / 6998 (0.06%) |  |  |
| occurrences (all)                  | 4                |  |  |
| Hyperkalaemia                      |                  |  |  |
| subjects affected / exposed        | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                  | 1                |  |  |
| Hypoglycaemia                      |                  |  |  |
| subjects affected / exposed        | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                  | 1                |  |  |
| Hypokalaemia                       |                  |  |  |
| subjects affected / exposed        | 1 / 6998 (0.01%) |  |  |
| occurrences (all)                  | 1                |  |  |
| Increased appetite                 |                  |  |  |



|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 6998 (0.01%) |  |  |
| occurrences (all)           | 1                |  |  |
| Type 2 diabetes mellitus    |                  |  |  |
| subjects affected / exposed | 1 / 6998 (0.01%) |  |  |
| occurrences (all)           | 1                |  |  |
| Vitamin D deficiency        |                  |  |  |
| subjects affected / exposed | 6 / 6998 (0.09%) |  |  |
| occurrences (all)           | 6                |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 23 April 2012    | change of inclusion and exclusion criteria with regards to cardiac risk patients and inclusion of further criteria for study drug discontinuation;<br>inclusion of the most recent recommendations from EMA in terms of cardiac response<br>monitoring following the first dose of fingolimod (April 20, 2012)                                                                                                                                                                                                               |
| 26 March 2013    | implementation of an update to the Gilenya® (fingolimod) label in the EU approved by the CHMP;<br>as the incidence of cardiac events after enrolling 1000 patients was found to be significantly lower than the incidence from recent studies which was the basis for the initial sample size calculation, the sample size needed to be increased from 2000 to a flexible sample size ranging from 3800 to 7000 patients with a fixed study termination by end of 2015                                                       |
| 20 March 2014    | implementation of a further update to the Gilenya® (fingolimod) label regarding interruption and restart of fingolimod real-life data: inter-patient regarding the incidence of bradycardia and bradyarrhythmic ECG events of patients who paused fingolimod treatment in comparison to fingolimod-naïve patients, treated for the first time in the START study, as well as within-patient comparisons for patients formerly treated with fingolimod within the START study.                                                |
| 24 April 2014    | Correction of minor errors in version 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 20 July 2014     | Clarification of the handling of safety cases for patients participating in both the interventional study START and the non-interventional study PASSAGE, thereby ensuring compliance with both the GCP regulations (START) and the modified regulations of the good pharmacovigilance practices module (specifically VI).                                                                                                                                                                                                   |
| 11 May 2015      | Addition of the same procedure as defined in amendment 5 for the PASSAGE study for patients participating in the PANGAEA 2.0 study;<br>Change of the definition of bradycardia from <40 bpm to <45 beats per minute to harmonize with the current Gilenya® label in the EU;<br>Removal of the exploratory endpoints regarding a sub-population of patients receiving a 24-hour monitoring due to low recruitment in this subgroup;<br>Extension of fixed recruitment end to June 2016 to enroll approximately 7000 patients. |
| 11 November 2015 | implementation of an update to the Gilenya® (fingolimod) label in the EU approved by the CHMP. The CHMP adopted a change to the existing indication to reflect a modification in the criteria for disease activity that needed to be fulfilled in order to enable a switch from a first line disease modifying therapy to Gilenya®. Hence, inclusion criterion #3 was adapted accordingly                                                                                                                                    |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported