



## Clinical trial results:

**An Extension Study to the CBAF312A2201 study to evaluate long-term safety, tolerability and efficacy of BAF312 given orally once daily in patients with relapsing-remitting multiple sclerosis**

### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2009-014392-51    |
| Trial protocol           | ES HU DE PL IT FI |
| Global end of trial date | 10 October 2016   |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 26 October 2017 |
| First version publication date | 26 October 2017 |

### Trial information

#### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | CBAF312A2201E1 |
|-----------------------|----------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01185821 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

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

Notes:

### Paediatric regulatory details

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

Notes:

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**Results analysis stage**

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|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 10 October 2016 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 10 October 2016 |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 10 October 2016 |
| Was the trial ended prematurely?                     | Yes             |

Notes:

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**General information about the trial**

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Main objective of the trial:

The primary objective was to evaluate long-term safety and tolerability of siponimod in relapsing-remitting multiple sclerosis (RRMS) patients, with specific emphasis on: effects on cardiac conduction during the titration of the study drug, long-term blood pressure effects, viral infections, macular edema, dermatologic alterations

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                          | 30 August 2010 |
| Long term follow-up planned                               | No             |
| Independent data monitoring committee (IDMC) involvement? | Yes            |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Canada: 11             |
| Country: Number of subjects enrolled | Finland: 8             |
| Country: Number of subjects enrolled | Germany: 27            |
| Country: Number of subjects enrolled | Hungary: 21            |
| Country: Number of subjects enrolled | Italy: 34              |
| Country: Number of subjects enrolled | Norway: 5              |
| Country: Number of subjects enrolled | Poland: 16             |
| Country: Number of subjects enrolled | Russian Federation: 15 |
| Country: Number of subjects enrolled | Spain: 13              |
| Country: Number of subjects enrolled | Switzerland: 8         |
| Country: Number of subjects enrolled | Turkey: 5              |
| Country: Number of subjects enrolled | United States: 21      |
| Worldwide total number of subjects   | 184                    |
| EEA total number of subjects         | 124                    |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 184 |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

All patients enrolled in the Extension study had completed the Core study. All patients underwent a 10 day titration at the start of the dose blinded phase of the study

### Pre-assignment

Screening details:

During the double blind phase of the extension study patients received the same dose from the Core study. Placebo patients from Core Period 1 were randomized to 0.5, 2 or 10mg, those from Period 2 were randomized to 0.25 or 1.25 mg. All patients received 2mg in Open Label phase (.5 and .25mg were titrated up to 2mg)

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | Overall Study (overall period)                         |
| Is this the baseline period? | Yes  |
| Allocation method            | Randomised - controlled                                |
| Blinding used                | Double blind   |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Assessor |

### Arms

|                              |                   |
|------------------------------|-------------------|
| Are arms mutually exclusive? | Yes               |
| <b>Arm title</b>             | BAF312 10 mg/2 mg |

Arm description:

10 mg dose in Double Blind Phase and 2 mg in Open Label Phase

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | siponimod          |
| Investigational medicinal product code | BAF312             |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

10 mg dose in Double Blind and 2 mg dose in Open Label dosed once a day

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | BAF312 2 mg/2 mg |
|------------------|------------------|

Arm description:

2 mg dose in Double Blind Phase and 2 mg in Open Label Phase

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | siponimod          |
| Investigational medicinal product code | BAF312             |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

2 mg dose in Double Blind and 2 mg dose in Open Label dosed once a day

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | BAF312 1.25 mg/2 mg |
|------------------|---------------------|

Arm description:

1.25 mg dose in Double Blind Phase and 2 mg in Open Label Phase

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

|   |                    |
|---|--------------------|
| Investigational medicinal product name                                    | siponimod          |
| Investigational medicinal product code                                    | BAF312             |
| Other name  |                    |
| Pharmaceutical forms  | Film-coated tablet |
| Routes of administration  | Oral use           |
| Dosage and administration details:  |                    |
| 1.25 mg dose in Double Blind and 2 mg dose in Open Label dosed once a day |                    |
| <b>Arm title</b>  | BAF312 .5 mg/2 mg  |
| Arm description:  |                    |
| .5 mg dose in Double Blind Phase and 2 mg in Open Label Phase             |                    |
| Arm type  | Experimental       |
| Investigational medicinal product name                                    | siponimod          |
| Investigational medicinal product code                                    | BAF312             |
| Other name  |                    |
| Pharmaceutical forms  | Film-coated tablet |
| Routes of administration  | Oral use           |
| Dosage and administration details:  |                    |
| .5 mg dose in Double Blind and 2 mg dose in Open Label dosed once a day   |                    |
| <b>Arm title</b>  | BAF312 .25 mg/2 mg |
| Arm description:  |                    |
| .25 mg dose in Double Blind Phase and 2 mg in Open Label Phase            |                    |
| Arm type  | Experimental       |
| Investigational medicinal product name                                    | siponimod          |
| Investigational medicinal product code                                    | BAF312             |
| Other name  |                    |
| Pharmaceutical forms  | Film-coated tablet |
| Routes of administration  | Oral use           |
| Dosage and administration details:  |                    |
| .25 mg dose in Double Blind and 2 mg dose in Open Label dosed once a day  |                    |

| <b>Number of subjects in period 1</b> | BAF312 10 mg/2 mg | BAF312 2 mg/2 mg | BAF312 1.25 mg/2 mg |
|---------------------------------------|-------------------|------------------|---------------------|
| Started                               | 33                | 29               | 43                  |
| Patients with washout                 | 33                | 29               | 39                  |
| Patients without washout              | 0 <sup>[1]</sup>  | 0 <sup>[2]</sup> | 4 <sup>[3]</sup>    |
| Patients on placebo in Core           | 8 <sup>[4]</sup>  | 7 <sup>[5]</sup> | 9 <sup>[6]</sup>    |
| Completed                             | 26                | 20               | 33                  |
| Not completed                         | 7                 | 9                | 10                  |
| Abnormal laboratory value(s)          | 1                 | 2                | 1                   |
| Adverse event, serious fatal          | -                 | 1                | -                   |
| Consent withdrawn by subject          | 3                 | 2                | 2                   |
| Adverse event, non-fatal              | 2                 | 3                | 1                   |
| Administrative problems               | -                 | -                | 1                   |
| Lost to follow-up                     | 1                 | 1                | 2                   |

|   |   |   |   |
|---|---|---|---|
| Condition no longer required study drug | - | - | - |
| Abnormal test procedure result          | - | - | - |
| Lack of efficacy                        | - | - | 3 |
| Protocol deviation                      | - | - | - |

| <b>Number of subjects in period 1</b>   | BAF312 .5 mg/2 mg | BAF312 .25 mg/2 mg |
|---|-------------------|--------------------|
| Started                                 | 29                | 50                 |
| Patients with washout                   | 29                | 33                 |
| Patients without washout                | 0 <sup>[7]</sup>  | 17 <sup>[8]</sup>  |
| Patients on placebo in Core             | 8 <sup>[9]</sup>  | 2 <sup>[10]</sup>  |
| Completed                               | 23                | 26                 |
| Not completed                           | 6                 | 24                 |
| Abnormal laboratory value(s)            | -                 | -                  |
| Adverse event, serious fatal            | -                 | -                  |
| Consent withdrawn by subject            | 1                 | 3                  |
| Adverse event, non-fatal                | 2                 | 5                  |
| Administrative problems                 | 1                 | 2                  |
| Lost to follow-up                       | 1                 | 2                  |
| Condition no longer required study drug | -                 | 1                  |
| Abnormal test procedure result          | -                 | 1                  |
| Lack of efficacy                        | -                 | 9                  |
| Protocol deviation                      | 1                 | 1                  |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Milestone added to provide additional information for patients entering the Extension study from the Core study.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Milestone added to provide additional information for patients entering the Extension study from the Core study.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Milestone added to provide additional information for patients entering the Extension study from the Core study.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Milestone added to provide additional information for patients entering the Extension study from the Core study.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Milestone added to provide additional information for patients entering the Extension study from the Core study.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the

arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Milestone added to provide additional information for patients entering the Extension study from the Core study.

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Milestone added to provide additional information for patients entering the Extension study from the Core study.

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Milestone added to provide additional information for patients entering the Extension study from the Core study.

[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Milestone added to provide additional information for patients entering the Extension study from the Core study.

[10] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Milestone added to provide additional information for patients entering the Extension study from the Core study.

## Baseline characteristics

### Reporting groups

|   |                     |
|---|---------------------|
| Reporting group title   | BAF312 10 mg/2 mg   |
| Reporting group description:<br>10 mg dose in Double Blind Phase and 2 mg in Open Label Phase   |                     |
| Reporting group title   | BAF312 2 mg/2 mg    |
| Reporting group description:<br>2 mg dose in Double Blind Phase and 2 mg in Open Label Phase    |                     |
| Reporting group title   | BAF312 1.25 mg/2 mg |
| Reporting group description:<br>1.25 mg dose in Double Blind Phase and 2 mg in Open Label Phase |                     |
| Reporting group title   | BAF312 .5 mg/2 mg   |
| Reporting group description:<br>.5 mg dose in Double Blind Phase and 2 mg in Open Label Phase   |                     |
| Reporting group title   | BAF312 .25 mg/2 mg  |
| Reporting group description:<br>.25 mg dose in Double Blind Phase and 2 mg in Open Label Phase  |                     |

| Reporting group values  | BAF312 10 mg/2 mg | BAF312 2 mg/2 mg | BAF312 1.25 mg/2 mg |
|---|-------------------|------------------|---------------------|
| Number of subjects  | 33                | 29               | 43                  |
| Age categorical<br>Units: Subjects  |                   |                  |                     |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                   |                  |                     |
| Age Continuous<br>Units: years  |                   |                  |                     |
| arithmetic mean   | 36.8              | 35.1             | 34.0                |
| standard deviation  | ± 9.09            | ± 9.16           | ± 7.57              |
| Gender, Male/Female<br>Units: Subjects  |                   |                  |                     |
| Female  | 21                | 18               | 32                  |
| Male  | 12                | 11               | 11                  |
| Study Specific Characteristic   Expanded disability status scale (EDSS)   |                   |                  |                     |
| Disability progression was assessed based on the EDSS scores ranging from 0 (normal) to 10 (death due to MS)  |                   |                  |                     |
| Units: Combined scores  |                   |                  |                     |
| arithmetic mean   | 2.03              | 2.19             | 1.95                |
| standard deviation  | ± 0.960           | ± 1.278          | ± 1.096             |



| <b>Reporting group values</b>  | BAF312 .5 mg/2 mg | BAF312 .25 mg/2 mg | Total |
|--|-------------------|--------------------|-------|
| Number of subjects   | 29                | 50                 | 184   |
| Age categorical<br>Units: Subjects   |                   |                    |       |
| In utero   |                   |                    | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks)  |                   |                    | 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)   |                   |                    | 0     |
| From 65-84 years   |                   |                    | 0     |
| 85 years and over  |                   |                    | 0     |
| Age Continuous<br>Units: years   |                   |                    |       |
| arithmetic mean  | 35.2              | 37.2               |       |
| standard deviation   | ± 9.10            | ± 8.42             | -     |
| Gender, Male/Female<br>Units: Subjects   |                   |                    |       |
| Female   | 18                | 41                 | 130   |
| Male   | 11                | 9                  | 54    |
| Study Specific Characteristic   Expanded disability status scale (EDSS)                                      |                   |                    |       |
| Disability progression was assessed based on the EDSS scores ranging from 0 (normal) to 10 (death due to MS) |                   |                    |       |
| Units: Combined scores   |                   |                    |       |
| arithmetic mean  | 1.88              | 2.22               |       |
| standard deviation   | ± 1.374           | ± 1.258            | -     |

## End points

### End points reporting groups

|   |                     |
|---|---------------------|
| Reporting group title   | BAF312 10 mg/2 mg   |
| Reporting group description:<br>10 mg dose in Double Blind Phase and 2 mg in Open Label Phase   |                     |
| Reporting group title   | BAF312 2 mg/2 mg    |
| Reporting group description:<br>2 mg dose in Double Blind Phase and 2 mg in Open Label Phase    |                     |
| Reporting group title   | BAF312 1.25 mg/2 mg |
| Reporting group description:<br>1.25 mg dose in Double Blind Phase and 2 mg in Open Label Phase |                     |
| Reporting group title   | BAF312 .5 mg/2 mg   |
| Reporting group description:<br>.5 mg dose in Double Blind Phase and 2 mg in Open Label Phase   |                     |
| Reporting group title   | BAF312 .25 mg/2 mg  |
| Reporting group description:<br>.25 mg dose in Double Blind Phase and 2 mg in Open Label Phase  |                     |

### Primary: Total number of adverse events during evaluation of long term safety and tolerability of BAF312A in Extension study.

|   |   |
|---|---|
| End point title   | Total number of adverse events during evaluation of long term safety and tolerability of BAF312A in Extension study. <sup>[1]</sup> |
| End point description:<br>Refer to adverse events for complete listing of serious adverse events and other adverse events.<br>Adverse events of interest were presented in separate tables. There were no reports of macular edema. |   |
| End point type  | Primary   |
| End point timeframe:<br>Baseline up to approximately 5 years  |   |

#### 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: No statistical analyses for this end point

| End point values            | BAF312 10 mg/2 mg | BAF312 2 mg/2 mg | BAF312 1.25 mg/2 mg | BAF312 .5 mg/2 mg |
|-----------------------------|-------------------|------------------|---------------------|-------------------|
| Subject group type          | Reporting group   | Reporting group  | Reporting group     | Reporting group   |
| Number of subjects analysed | 33                | 29               | 43                  | 29                |
| Units: events               |                   |                  |                     |                   |
| Serious adverse events      | 4                 | 7                | 6                   | 6                 |
| Other adverse events        | 30                | 26               | 42                  | 29                |

| End point values            | BAF312 .25 mg/2 mg |  |  |  |
|-----------------------------|--------------------|--|--|--|
| Subject group type          | Reporting group    |  |  |  |
| Number of subjects analysed | 50                 |  |  |  |
| Units: events               |                    |  |  |  |
| Serious adverse events      | 8                  |  |  |  |

|                      |    |  |  |  |
|----------------------|----|--|--|--|
| Other adverse events | 42 |  |  |  |
|----------------------|----|--|--|--|

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of participants with cardiac conduction abnormalities during the titration phase of the study

|                 |   |
|-----------------|---|
| End point title | Number of participants with cardiac conduction abnormalities during the titration phase of the study <sup>[2]</sup> |
|-----------------|---|

End point description:

Number of patients with abnormal ECG conduction findings during dose-blinded titration at any visit post-dose, by type of abnormality and treatment (Extension Set). Number analyzed represent participants who had ECG results. Washout was defined as not being on treatment drug between Core and Extension for >7 days. Abbreviations: washout = WO, Con=conduction

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

End point timeframe:

Baseline Extension up to day 10

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: No statistical analyses for this end point

| End point values                                  | BAF312 10 mg/2 mg | BAF312 2 mg/2 mg | BAF312 1.25 mg/2 mg | BAF312 .5 mg/2 mg |
|---|-------------------|------------------|---------------------|-------------------|
| Subject group type                                | Reporting group   | Reporting group  | Reporting group     | Reporting group   |
| Number of subjects analysed                       | 33                | 29               | 39                  | 29                |
| Units: participants                               |                   |                  |                     |                   |
| With WO (33,29,39,29,33) Conduction-Prolonged QTc | 5                 | 2                | 5                   | 2                 |
| With washout (33,29,39,29,33) Conduction - IVCD   | 3                 | 8                | 1                   | 3                 |
| With WO (33,29,39,29,33) Conduction - AV Mobitz I | 1                 | 0                | 0                   | 0                 |
| With WO (33,29,39,29,33) Con:1st degree AV block  | 0                 | 1                | 1                   | 1                 |
| With washout (33,29,39,29,33) Conduction - WPW    | 0                 | 0                | 0                   | 1                 |
| Without washout (0,0,4,0,17) Conduction - IVCD    | 0                 | 0                | 0                   | 0                 |

| End point values                                  | BAF312 .25 mg/2 mg |  |  |  |
|---|--------------------|--|--|--|
| Subject group type                                | Reporting group    |  |  |  |
| Number of subjects analysed                       | 33                 |  |  |  |
| Units: participants                               |                    |  |  |  |
| With WO (33,29,39,29,33) Conduction-Prolonged QTc | 4                  |  |  |  |

|  |   |  |  |  |
|--|---|--|--|--|
| With washout (33,29,39,29,33)<br>Conduction - IVCD   | 0 |  |  |  |
| With WO (33,29,39,29,33) Conduction -<br>AV Mobitz I | 0 |  |  |  |
| With WO (33,29,39,29,33) Con:1st<br>degree AV block  | 1 |  |  |  |
| With washout (33,29,39,29,33)<br>Conduction - WPW    | 0 |  |  |  |
| Without washout (0,0,4,0,17)<br>Conduction - IVCD    | 4 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of participants with changes in blood pressure for overall extension study. (Extension analysis set)

|                 |  |
|-----------------|--|
| End point title | Number of participants with changes in blood pressure for overall extension study. (Extension analysis set) <sup>[3]</sup> |
|-----------------|--|

End point description:

Sitting blood pressure was measured in triplicate. The categories of notably low and high values and changes are presented for systolic (SBP) and diastolic (DBP). Multiple occurrences for a patient are counted as one occurrence in this table.

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

End point timeframe:

Baseline Extension up to approximately 5 years

Notes:

[3] - 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: No statistical analyses for this end point

| End point values                | BAF312 10<br>mg/2 mg | BAF312 2 mg/2<br>mg | BAF312 1.25<br>mg/2 mg | BAF312 .5<br>mg/2 mg |
|---------------------------------|----------------------|---------------------|------------------------|----------------------|
| Subject group type              | Reporting group      | Reporting group     | Reporting group        | Reporting group      |
| Number of subjects analysed     | 33                   | 29                  | 43                     | 29                   |
| Units: participants             |                      |                     |                        |                      |
| SBP Low: ≤ 90                   | 1                    | 3                   | 2                      | 1                    |
| SBP ≥ 20 decrease from baseline | 8                    | 10                  | 4                      | 6                    |
| SBP High: ≥ 160                 | 1                    | 1                   | 1                      | 3                    |
| SBP ≥ 20 increase from baseline | 9                    | 8                   | 12                     | 13                   |
| DBP Low: ≤ 50                   | 1                    | 0                   | 1                      | 0                    |
| DBP ≥ 15 decrease from baseline | 14                   | 8                   | 10                     | 10                   |
| DBP High: ≥ 100                 | 4                    | 7                   | 4                      | 4                    |
| DBP ≥ 15 increase from baseline | 9                    | 13                  | 13                     | 11                   |

| End point values            | BAF312 .25<br>mg/2 mg |  |  |  |
|-----------------------------|-----------------------|--|--|--|
| Subject group type          | Reporting group       |  |  |  |
| Number of subjects analysed | 50                    |  |  |  |
| Units: participants         |                       |  |  |  |

|                                      |    |  |  |  |
|--------------------------------------|----|--|--|--|
| SBP Low: $\leq 90$                   | 1  |  |  |  |
| SBP $\geq 20$ decrease from baseline | 10 |  |  |  |
| SBP High: $\geq 160$                 | 3  |  |  |  |
| SBP $\geq 20$ increase from baseline | 18 |  |  |  |
| DBP Low: $\leq 50$                   | 1  |  |  |  |
| DBP $\geq 15$ decrease from baseline | 10 |  |  |  |
| DBP High: $\geq 100$                 | 4  |  |  |  |
| DBP $\geq 15$ increase from baseline | 17 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of participants with viral infections of interest greater or equal to 5% in any dose group (Extension Set)

|                 |  |
|-----------------|--|
| End point title | Number of participants with viral infections of interest greater or equal to 5% in any dose group (Extension Set) <sup>[4]</sup> |
|-----------------|--|

End point description:

Most infections were clinical diagnoses and were not confirmed by microbiology / virologic investigations. A patient with multiple occurrences of an infection for a preferred term is counted only once in each specific category. Events identified as infections by the Investigator and defined as an AE with onset on or after the first dose of Extension Study drug up to and including 30 days after the date of the last dose

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

End point timeframe:

Baseline Extension up to approximately 5 years

Notes:

[4] - 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: No statistical analyses for this end point

| End point values            | BAF312 10 mg/2 mg | BAF312 2 mg/2 mg | BAF312 1.25 mg/2 mg | BAF312 .5 mg/2 mg |
|-----------------------------|-------------------|------------------|---------------------|-------------------|
| Subject group type          | Reporting group   | Reporting group  | Reporting group     | Reporting group   |
| Number of subjects analysed | 33                | 29               | 43                  | 29                |
| Units: participants         |                   |                  |                     |                   |
| Oral herpes                 | 5                 | 0                | 4                   | 2                 |
| Herpes zoster               | 5                 | 0                | 3                   | 2                 |
| Influenza                   | 3                 | 4                | 3                   | 6                 |

| End point values            | BAF312 .25 mg/2 mg |  |  |  |
|-----------------------------|--------------------|--|--|--|
| Subject group type          | Reporting group    |  |  |  |
| Number of subjects analysed | 50                 |  |  |  |
| Units: participants         |                    |  |  |  |
| Oral herpes                 | 4                  |  |  |  |
| Herpes zoster               | 0                  |  |  |  |
| Influenza                   | 6                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of participants with dermatologic alterations - basal cell carcinoma (Extension Set)

|                 |  |
|-----------------|--|
| End point title | Number of participants with dermatologic alterations - basal cell carcinoma (Extension Set) <sup>[5]</sup> |
|-----------------|--|

End point description:

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

End point timeframe:

Baseline Extension up to approximately 5 years

Notes:

[5] - 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: No statistical analyses for this end point

| End point values            | BAF312 10 mg/2 mg | BAF312 2 mg/2 mg | BAF312 1.25 mg/2 mg | BAF312 .5 mg/2 mg |
|-----------------------------|-------------------|------------------|---------------------|-------------------|
| Subject group type          | Reporting group   | Reporting group  | Reporting group     | Reporting group   |
| Number of subjects analysed | 33                | 29               | 43                  | 29                |
| Units: participants         | 1                 | 0                | 1                   | 0                 |

| End point values            | BAF312 .25 mg/2 mg |  |  |  |
|-----------------------------|--------------------|--|--|--|
| Subject group type          | Reporting group    |  |  |  |
| Number of subjects analysed | 50                 |  |  |  |
| Units: participants         | 1                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of relapses in one year - annualized relapse rates for overall extension study (ARR) (Extension Set)

|                 |   |
|-----------------|---|
| End point title | Number of relapses in one year - annualized relapse rates for overall extension study (ARR) (Extension Set) |
|-----------------|---|

End point description:

Group level ARR (raw) is calculated as the total number of relapses for all the patients in the treatment group divided by the total number of days on study for all patients in the group and multiplied by 365.25 to obtain the annual rate. Model estimates are based on a negative binomial regression model, adjusted for treatment group, age, baseline EDSS, baseline number of Gd-enhanced T1 lesions and

number of relapses in previous 2 years as covariates, with log(time on study in years) as the offset variable, using the log link.

|  |           |
|--|-----------|
| End point type                                 | Secondary |
| End point timeframe:                           |           |
| Baseline extension up to approximately 5 years |           |

| End point values                          | BAF312 10 mg/2 mg   | BAF312 2 mg/2 mg    | BAF312 1.25 mg/2 mg | BAF312 .5 mg/2 mg   |
|---|---------------------|---------------------|---------------------|---------------------|
| Subject group type                        | Reporting group     | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed               | 33                  | 29                  | 43                  | 29                  |
| Units: Group level ARR                    |                     |                     |                     |                     |
| arithmetic mean (confidence interval 95%) | 0.18 (0.11 to 0.31) | 0.15 (0.08 to 0.26) | 0.16 (0.10 to 0.26) | 0.19 (0.11 to 0.33) |

| End point values                          | BAF312 .25 mg/2 mg  |  |  |  |
|---|---------------------|--|--|--|
| Subject group type                        | Reporting group     |  |  |  |
| Number of subjects analysed               | 50                  |  |  |  |
| Units: Group level ARR                    |                     |  |  |  |
| arithmetic mean (confidence interval 95%) | 0.22 (0.14 to 0.35) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants free of Magnetic Resonance Imaging (MRI) identified disease activity at any scan during Extension Study (Extension Set)

|                 |  |
|-----------------|--|
| End point title | Percentage of participants free of Magnetic Resonance Imaging (MRI) identified disease activity at any scan during Extension Study (Extension Set) |
|-----------------|--|

End point description:

Free of MRI disease activity is defined as free of Gadolinium enhanced T1 lesions at any scan; free of new or enlarging T2 lesions at any scan: free of both gadolinium enhanced T1 lesions and new or enlarging T2 lesions at any sca, N = Number of patients with at least one MRI scan during the specified time period. New lesions at a specific visit are assessed relative to the previous scheduled visit scan. No imputation of missing scans is performed. As a result missing scans can lead to an overestimation of the proportion of patients free of a specific MRI activity.

|  |           |
|--|-----------|
| End point type                                 | Secondary |
| End point timeframe:                           |           |
| Baseline Extension up to approximately 5 years |           |

| End point values                                   | BAF312 10 mg/2 mg | BAF312 2 mg/2 mg | BAF312 1.25 mg/2 mg | BAF312 .5 mg/2 mg |
|--|-------------------|------------------|---------------------|-------------------|
| Subject group type                                 | Reporting group   | Reporting group  | Reporting group     | Reporting group   |
| Number of subjects analysed                        | 31                | 26               | 43                  | 29                |
| Units: percentage of participants                  |                   |                  |                     |                   |
| number (not applicable)                            |                   |                  |                     |                   |
| Free of Gd-enhanced T1 lesions at any scan         | 58.1              | 57.7             | 58.1                | 44.8              |
| Free of new/enlarging T2 lesions at any scan       | 32.3              | 42.3             | 46.5                | 20.7              |
| Free of Gd-enhanced T1 and new enlarged T2 lesions | 32.3              | 42.3             | 44.2                | 20.7              |

| End point values                                   | BAF312 .25 mg/2 mg |  |  |  |
|--|--------------------|--|--|--|
| Subject group type                                 | Reporting group    |  |  |  |
| Number of subjects analysed                        | 47                 |  |  |  |
| Units: percentage of participants                  |                    |  |  |  |
| number (not applicable)                            |                    |  |  |  |
| Free of Gd-enhanced T1 lesions at any scan         | 66.0               |  |  |  |
| Free of new/enlarging T2 lesions at any scan       | 40.4               |  |  |  |
| Free of Gd-enhanced T1 and new enlarged T2 lesions | 40.4               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants free of confirmed disability progression in Extension Study (Extension Set)

|                 |  |
|-----------------|--|
| End point title | Percentage of participants free of confirmed disability progression in Extension Study (Extension Set) |
|-----------------|--|

End point description:

Six-month disability progression was defined relative to extension baseline EDSS score: 1.5 point increase in patients with baseline EDSS score of 0, 1.0 increase in patients with baseline EDSS score of between 0.5 to 5.0, inclusive and 0.5 increase in patients with baseline EDSS score of  $\geq 5.5$ . The criteria for 6-month disability progression included detection of onset of progression and confirmation of progression for a period of at least 6 months.

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

End point timeframe:

Baseline Extension up to approximately 5 years



| <b>End point values</b>           | BAF312 10 mg/2 mg   | BAF312 2 mg/2 mg    | BAF312 1.25 mg/2 mg | BAF312 .5 mg/2 mg   |
|-----------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type                | Reporting group     | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed       | 33                  | 29                  | 43                  | 29                  |
| Units: percentage of participants |                     |                     |                     |                     |
| number (confidence interval 95%)  | 72.3 (56.0 to 88.7) | 82.4 (66.6 to 98.3) | 84.8 (73.5 to 96.0) | 81.4 (66.6 to 96.1) |

| <b>End point values</b>           | BAF312 .25 mg/2 mg  |  |  |  |
|-----------------------------------|---------------------|--|--|--|
| Subject group type                | Reporting group     |  |  |  |
| Number of subjects analysed       | 50                  |  |  |  |
| Units: percentage of participants |                     |  |  |  |
| number (confidence interval 95%)  | 78.6 (65.4 to 91.9) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | BAF312 10/2 mg |
|-----------------------|----------------|

Reporting group description:

BAF312 10/2 mg

|                       |               |
|-----------------------|---------------|
| Reporting group title | BAF312 2/2 mg |
|-----------------------|---------------|

Reporting group description:

BAF312 2/2 mg

|                       |                  |
|-----------------------|------------------|
| Reporting group title | BAF312 1.25/2 mg |
|-----------------------|------------------|

Reporting group description:

BAF312 1.25/2 mg

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | BAF312 0.5/2 mg |
|-----------------------|-----------------|

Reporting group description:

BAF312 0.5/2 mg

|                       |                  |
|-----------------------|------------------|
| Reporting group title | BAF312 0.25/2 mg |
|-----------------------|------------------|

Reporting group description:

BAF312 0.25/2 mg

|                       |              |
|-----------------------|--------------|
| Reporting group title | All patients |
|-----------------------|--------------|

Reporting group description:

All patients

| Serious adverse events  | BAF312 10/2 mg  | BAF312 2/2 mg   | BAF312 1.25/2 mg |
|---|-----------------|-----------------|------------------|
| Total subjects affected by serious adverse events                   |                 |                 |                  |
| subjects affected / exposed   | 4 / 33 (12.12%) | 7 / 29 (24.14%) | 6 / 43 (13.95%)  |
| number of deaths (all causes)                                       | 0               | 1               | 0                |
| number of deaths resulting from adverse events                      | 0               | 0               | 0                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                 |                  |
| Basal cell carcinoma  |                 |                 |                  |
| subjects affected / exposed   | 1 / 33 (3.03%)  | 0 / 29 (0.00%)  | 1 / 43 (2.33%)   |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0           | 0 / 2            |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0            |
| Breast cancer   |                 |                 |                  |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Colon cancer metastatic                              |                |                |                |
| subjects affected / exposed                          | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Pregnancy, puerperium and perinatal conditions       |                |                |                |
| Abortion   |                |                |                |
| subjects affected / exposed                          | 0 / 33 (0.00%) | 1 / 29 (3.45%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| Submandibular mass                                   |                |                |                |
| subjects affected / exposed                          | 1 / 33 (3.03%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Immune system disorders                              |                |                |                |
| Anaphylactic reaction                                |                |                |                |
| subjects affected / exposed                          | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Reproductive system and breast disorders             |                |                |                |
| Benign prostatic hyperplasia                         |                |                |                |
| subjects affected / exposed                          | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Metrorrhagia   |                |                |                |
| subjects affected / exposed                          | 1 / 33 (3.03%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Uterine cervical metaplasia                          |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Psychiatric disorders                           |                |                |                |
| Depression                                      |                |                |                |
| subjects affected / exposed                     | 1 / 33 (3.03%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Drug abuse                                      |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Mental disorder                                 |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Investigations                                  |                |                |                |
| Smear cervix abnormal                           |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications  |                |                |                |
| Ankle fracture                                  |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Craniocerebral injury                           |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 1 / 29 (3.45%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Femur fracture                                  |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 1 / 29 (3.45%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Tendon rupture                                  |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Dysaesthesia                                    |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Generalised tonic-clonic seizure                |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 1 / 29 (3.45%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Headache  |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Multiple sclerosis relapse                      |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Sciatica  |                |                |                |
| subjects affected / exposed                     | 1 / 33 (3.03%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Seizure   |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 1 / 29 (3.45%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| Splenic cyst                                    |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Ear and labyrinth disorders                     |                |                |                |
| Otosclerosis                                    |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Eye disorders                                   |                |                |                |
| Glaucoma  |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Abdominal discomfort                            |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 1 / 29 (3.45%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastritis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 1 / 29 (3.45%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nausea  |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pancreatitis acute                              |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Vomiting  |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatobiliary disorders                         |                |                |                |
| Biliary dyskinesia                              |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 33 (0.00%) | 1 / 29 (3.45%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| Stress urinary incontinence                     |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Oral herpes                                     |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pyelonephritis                                  |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pyelonephritis acute                            |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory tract infection                     |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Upper respiratory tract infection               |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urinary tract infection                         |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Decreased appetite                              |                |                |                |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>                                       | BAF312 0.5/2 mg | BAF312 0.25/2 mg | All patients      |
|---|-----------------|------------------|-------------------|
| Total subjects affected by serious adverse events                   |                 |                  |                   |
| subjects affected / exposed   | 6 / 29 (20.69%) | 8 / 50 (16.00%)  | 31 / 184 (16.85%) |
| number of deaths (all causes)                                       | 0               | 0                | 1                 |
| number of deaths resulting from adverse events                      | 0               | 0                | 0                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                  |                   |
| Basal cell carcinoma  |                 |                  |                   |
| subjects affected / exposed   | 0 / 29 (0.00%)  | 0 / 50 (0.00%)   | 2 / 184 (1.09%)   |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0            | 0 / 3             |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0            | 0 / 0             |
| Breast cancer   |                 |                  |                   |
| subjects affected / exposed   | 0 / 29 (0.00%)  | 1 / 50 (2.00%)   | 2 / 184 (1.09%)   |
| occurrences causally related to treatment / all                     | 0 / 0           | 1 / 1            | 2 / 2             |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0            | 0 / 0             |
| Colon cancer metastatic   |                 |                  |                   |
| subjects affected / exposed   | 0 / 29 (0.00%)  | 1 / 50 (2.00%)   | 1 / 184 (0.54%)   |
| occurrences causally related to treatment / all                     | 0 / 0           | 1 / 1            | 1 / 1             |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0            | 0 / 0             |
| Pregnancy, puerperium and perinatal conditions                      |                 |                  |                   |
| Abortion  |                 |                  |                   |
| subjects affected / exposed   | 0 / 29 (0.00%)  | 0 / 50 (0.00%)   | 1 / 184 (0.54%)   |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0            | 0 / 0             |
| General disorders and administration site conditions                |                 |                  |                   |
| Submandibular mass  |                 |                  |                   |
| subjects affected / exposed   | 0 / 29 (0.00%)  | 0 / 50 (0.00%)   | 1 / 184 (0.54%)   |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0            | 0 / 0             |
| Immune system disorders   |                 |                  |                   |



|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Anaphylactic reaction                           |                |                |                 |
| subjects affected / exposed                     | 1 / 29 (3.45%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Reproductive system and breast disorders        |                |                |                 |
| Benign prostatic hyperplasia                    |                |                |                 |
| subjects affected / exposed                     | 1 / 29 (3.45%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Metrorrhagia                                    |                |                |                 |
| subjects affected / exposed                     | 0 / 29 (0.00%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Uterine cervical metaplasia                     |                |                |                 |
| subjects affected / exposed                     | 0 / 29 (0.00%) | 1 / 50 (2.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Psychiatric disorders                           |                |                |                 |
| Depression                                      |                |                |                 |
| subjects affected / exposed                     | 0 / 29 (0.00%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Drug abuse                                      |                |                |                 |
| subjects affected / exposed                     | 1 / 29 (3.45%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Mental disorder                                 |                |                |                 |
| subjects affected / exposed                     | 1 / 29 (3.45%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Investigations                                  |                |                |                 |
| Smear cervix abnormal                           |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                           | 0 / 29 (0.00%) | 1 / 50 (2.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Injury, poisoning and procedural complications</b> |                |                |                 |
| Ankle fracture  |                |                |                 |
| subjects affected / exposed                           | 1 / 29 (3.45%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all       | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0           |
| Craniocerebral injury                                 |                |                |                 |
| subjects affected / exposed                           | 0 / 29 (0.00%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 1           |
| Femur fracture  |                |                |                 |
| subjects affected / exposed                           | 0 / 29 (0.00%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0           |
| Tendon rupture  |                |                |                 |
| subjects affected / exposed                           | 0 / 29 (0.00%) | 1 / 50 (2.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Nervous system disorders</b>                       |                |                |                 |
| Dysaesthesia  |                |                |                 |
| subjects affected / exposed                           | 0 / 29 (0.00%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0           |
| Generalised tonic-clonic seizure                      |                |                |                 |
| subjects affected / exposed                           | 0 / 29 (0.00%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0           |
| Headache  |                |                |                 |
| subjects affected / exposed                           | 1 / 29 (3.45%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all       | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0           |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Multiple sclerosis relapse                      |                |                |                 |
| subjects affected / exposed                     | 0 / 29 (0.00%) | 2 / 50 (4.00%) | 3 / 184 (1.63%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2          | 1 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Sciatica  |                |                |                 |
| subjects affected / exposed                     | 0 / 29 (0.00%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Seizure   |                |                |                 |
| subjects affected / exposed                     | 0 / 29 (0.00%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Blood and lymphatic system disorders            |                |                |                 |
| Splenic cyst                                    |                |                |                 |
| subjects affected / exposed                     | 0 / 29 (0.00%) | 1 / 50 (2.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Ear and labyrinth disorders                     |                |                |                 |
| Otosclerosis                                    |                |                |                 |
| subjects affected / exposed                     | 1 / 29 (3.45%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Eye disorders                                   |                |                |                 |
| Glaucoma  |                |                |                 |
| subjects affected / exposed                     | 0 / 29 (0.00%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Gastrointestinal disorders                      |                |                |                 |
| Abdominal discomfort                            |                |                |                 |
| subjects affected / exposed                     | 0 / 29 (0.00%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Gastritis                                       |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 29 (0.00%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Nausea  |                |                |                 |
| subjects affected / exposed                     | 1 / 29 (3.45%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pancreatitis acute                              |                |                |                 |
| subjects affected / exposed                     | 1 / 29 (3.45%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Vomiting  |                |                |                 |
| subjects affected / exposed                     | 1 / 29 (3.45%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Hepatobiliary disorders                         |                |                |                 |
| Biliary dyskinesia                              |                |                |                 |
| subjects affected / exposed                     | 0 / 29 (0.00%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Renal and urinary disorders                     |                |                |                 |
| Stress urinary incontinence                     |                |                |                 |
| subjects affected / exposed                     | 0 / 29 (0.00%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Infections and infestations                     |                |                |                 |
| Oral herpes                                     |                |                |                 |
| subjects affected / exposed                     | 0 / 29 (0.00%) | 1 / 50 (2.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pyelonephritis                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 29 (0.00%) | 1 / 50 (2.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Pyelonephritis acute                            |                |                |                 |
| subjects affected / exposed                     | 0 / 29 (0.00%) | 1 / 50 (2.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Respiratory tract infection                     |                |                |                 |
| subjects affected / exposed                     | 0 / 29 (0.00%) | 1 / 50 (2.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Upper respiratory tract infection               |                |                |                 |
| subjects affected / exposed                     | 0 / 29 (0.00%) | 1 / 50 (2.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Urinary tract infection                         |                |                |                 |
| subjects affected / exposed                     | 0 / 29 (0.00%) | 1 / 50 (2.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2          | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Metabolism and nutrition disorders              |                |                |                 |
| Decreased appetite                              |                |                |                 |
| subjects affected / exposed                     | 1 / 29 (3.45%) | 0 / 50 (0.00%) | 1 / 184 (0.54%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |

Frequency threshold for reporting non-serious adverse events: 4 %

| <b>Non-serious adverse events</b>                                   | BAF312 10/2 mg   | BAF312 2/2 mg    | BAF312 1.25/2 mg |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events               |                  |                  |                  |
| subjects affected / exposed   | 30 / 33 (90.91%) | 26 / 29 (89.66%) | 42 / 43 (97.67%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                  |                  |
| Fibrous histiocytoma  |                  |                  |                  |
| subjects affected / exposed   | 0 / 33 (0.00%)   | 1 / 29 (3.45%)   | 3 / 43 (6.98%)   |
| occurrences (all)   | 0                | 1                | 3                |
| Melanocytic naevus  |                  |                  |                  |
| subjects affected / exposed   | 2 / 33 (6.06%)   | 1 / 29 (3.45%)   | 6 / 43 (13.95%)  |
| occurrences (all)   | 2                | 1                | 8                |
| Seborrhoeic keratosis   |                  |                  |                  |

|   |                     |                      |                      |
|---|---------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)  | 2 / 33 (6.06%)<br>2 | 1 / 29 (3.45%)<br>1  | 0 / 43 (0.00%)<br>0  |
| Skin papilloma<br>subjects affected / exposed<br>occurrences (all)  | 2 / 33 (6.06%)<br>2 | 3 / 29 (10.34%)<br>3 | 1 / 43 (2.33%)<br>1  |
| Uterine leiomyoma<br>subjects affected / exposed<br>occurrences (all)   | 2 / 33 (6.06%)<br>2 | 0 / 29 (0.00%)<br>0  | 0 / 43 (0.00%)<br>0  |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)                                  | 1 / 33 (3.03%)<br>2 | 1 / 29 (3.45%)<br>1  | 3 / 43 (6.98%)<br>3  |
| General disorders and administration<br>site conditions<br>Asthenia<br>subjects affected / exposed<br>occurrences (all) | 0 / 33 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1  | 2 / 43 (4.65%)<br>2  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)   | 1 / 33 (3.03%)<br>1 | 4 / 29 (13.79%)<br>6 | 5 / 43 (11.63%)<br>5 |
| Gait disturbance<br>subjects affected / exposed<br>occurrences (all)  | 3 / 33 (9.09%)<br>3 | 0 / 29 (0.00%)<br>0  | 0 / 43 (0.00%)<br>0  |
| Influenza like illness<br>subjects affected / exposed<br>occurrences (all)  | 1 / 33 (3.03%)<br>1 | 0 / 29 (0.00%)<br>0  | 2 / 43 (4.65%)<br>2  |
| Non-cardiac chest pain<br>subjects affected / exposed<br>occurrences (all)  | 3 / 33 (9.09%)<br>3 | 0 / 29 (0.00%)<br>0  | 1 / 43 (2.33%)<br>1  |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)   | 0 / 33 (0.00%)<br>0 | 2 / 29 (6.90%)<br>2  | 0 / 43 (0.00%)<br>0  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)   | 2 / 33 (6.06%)<br>3 | 1 / 29 (3.45%)<br>1  | 4 / 43 (9.30%)<br>5  |
| Respiratory, thoracic and mediastinal<br>disorders  |                     |                      |                      |

|                             |                |                 |                 |
|-----------------------------|----------------|-----------------|-----------------|
| Catarrh                     |                |                 |                 |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 29 (0.00%)  | 1 / 43 (2.33%)  |
| occurrences (all)           | 1              | 0               | 2               |
| Cough                       |                |                 |                 |
| subjects affected / exposed | 3 / 33 (9.09%) | 3 / 29 (10.34%) | 3 / 43 (6.98%)  |
| occurrences (all)           | 3              | 6               | 3               |
| Dyspnoea                    |                |                 |                 |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 29 (0.00%)  | 2 / 43 (4.65%)  |
| occurrences (all)           | 0              | 0               | 2               |
| Epistaxis                   |                |                 |                 |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 29 (0.00%)  | 0 / 43 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0               |
| Oropharyngeal pain          |                |                 |                 |
| subjects affected / exposed | 3 / 33 (9.09%) | 1 / 29 (3.45%)  | 3 / 43 (6.98%)  |
| occurrences (all)           | 3              | 1               | 3               |
| Rhinitis allergic           |                |                 |                 |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 29 (0.00%)  | 2 / 43 (4.65%)  |
| occurrences (all)           | 0              | 0               | 4               |
| Wheezing                    |                |                 |                 |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 29 (0.00%)  | 0 / 43 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0               |
| Psychiatric disorders       |                |                 |                 |
| Anxiety                     |                |                 |                 |
| subjects affected / exposed | 3 / 33 (9.09%) | 1 / 29 (3.45%)  | 1 / 43 (2.33%)  |
| occurrences (all)           | 3              | 2               | 1               |
| Depression                  |                |                 |                 |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 29 (3.45%)  | 6 / 43 (13.95%) |
| occurrences (all)           | 1              | 1               | 6               |
| Insomnia                    |                |                 |                 |
| subjects affected / exposed | 1 / 33 (3.03%) | 2 / 29 (6.90%)  | 8 / 43 (18.60%) |
| occurrences (all)           | 2              | 2               | 8               |
| Sleep disorder              |                |                 |                 |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 29 (3.45%)  | 0 / 43 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0               |
| Investigations              |                |                 |                 |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)  | 3 / 33 (9.09%)<br>5  | 5 / 29 (17.24%)<br>6 | 3 / 43 (6.98%)<br>3  |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)           | 0 / 33 (0.00%)<br>0  | 0 / 29 (0.00%)<br>0  | 0 / 43 (0.00%)<br>0  |
| Blood cholesterol increased<br>subjects affected / exposed<br>occurrences (all)         | 0 / 33 (0.00%)<br>0  | 0 / 29 (0.00%)<br>0  | 1 / 43 (2.33%)<br>1  |
| C-reactive protein increased<br>subjects affected / exposed<br>occurrences (all)        | 1 / 33 (3.03%)<br>1  | 1 / 29 (3.45%)<br>1  | 0 / 43 (0.00%)<br>0  |
| Gamma-glutamyltransferase increased<br>subjects affected / exposed<br>occurrences (all) | 3 / 33 (9.09%)<br>4  | 3 / 29 (10.34%)<br>4 | 2 / 43 (4.65%)<br>2  |
| Hepatic enzyme increased<br>subjects affected / exposed<br>occurrences (all)            | 2 / 33 (6.06%)<br>2  | 1 / 29 (3.45%)<br>1  | 1 / 43 (2.33%)<br>1  |
| Lymphocyte count decreased<br>subjects affected / exposed<br>occurrences (all)          | 4 / 33 (12.12%)<br>4 | 2 / 29 (6.90%)<br>2  | 4 / 43 (9.30%)<br>11 |
| Injury, poisoning and procedural complications  |                      |                      |                      |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                           | 2 / 33 (6.06%)<br>5  | 2 / 29 (6.90%)<br>3  | 0 / 43 (0.00%)<br>0  |
| Fall<br>subjects affected / exposed<br>occurrences (all)                                | 3 / 33 (9.09%)<br>3  | 3 / 29 (10.34%)<br>4 | 0 / 43 (0.00%)<br>0  |
| Joint injury<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 33 (3.03%)<br>1  | 0 / 29 (0.00%)<br>0  | 2 / 43 (4.65%)<br>2  |
| Ligament sprain<br>subjects affected / exposed<br>occurrences (all)                     | 2 / 33 (6.06%)<br>2  | 0 / 29 (0.00%)<br>0  | 2 / 43 (4.65%)<br>2  |
| Limb injury   |                      |                      |                      |



|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 33 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 | 0 / 43 (0.00%)<br>0 |
| Cardiac disorders                                |                     |                     |                     |
| Palpitations                                     |                     |                     |                     |
| subjects affected / exposed                      | 0 / 33 (0.00%)      | 2 / 29 (6.90%)      | 0 / 43 (0.00%)      |
| occurrences (all)                                | 0                   | 2                   | 0                   |
| Tachycardia                                      |                     |                     |                     |
| subjects affected / exposed                      | 0 / 33 (0.00%)      | 0 / 29 (0.00%)      | 1 / 43 (2.33%)      |
| occurrences (all)                                | 0                   | 0                   | 1                   |
| Nervous system disorders                         |                     |                     |                     |
| Burning sensation                                |                     |                     |                     |
| subjects affected / exposed                      | 0 / 33 (0.00%)      | 0 / 29 (0.00%)      | 1 / 43 (2.33%)      |
| occurrences (all)                                | 0                   | 0                   | 1                   |
| Dizziness  |                     |                     |                     |
| subjects affected / exposed                      | 1 / 33 (3.03%)      | 1 / 29 (3.45%)      | 1 / 43 (2.33%)      |
| occurrences (all)                                | 1                   | 1                   | 1                   |
| Headache   |                     |                     |                     |
| subjects affected / exposed                      | 9 / 33 (27.27%)     | 4 / 29 (13.79%)     | 9 / 43 (20.93%)     |
| occurrences (all)                                | 14                  | 7                   | 9                   |
| Hypoaesthesia                                    |                     |                     |                     |
| subjects affected / exposed                      | 1 / 33 (3.03%)      | 0 / 29 (0.00%)      | 0 / 43 (0.00%)      |
| occurrences (all)                                | 3                   | 0                   | 0                   |
| Migraine   |                     |                     |                     |
| subjects affected / exposed                      | 2 / 33 (6.06%)      | 0 / 29 (0.00%)      | 3 / 43 (6.98%)      |
| occurrences (all)                                | 2                   | 0                   | 3                   |
| Muscle spasticity                                |                     |                     |                     |
| subjects affected / exposed                      | 0 / 33 (0.00%)      | 2 / 29 (6.90%)      | 0 / 43 (0.00%)      |
| occurrences (all)                                | 0                   | 2                   | 0                   |
| Neuralgia  |                     |                     |                     |
| subjects affected / exposed                      | 1 / 33 (3.03%)      | 0 / 29 (0.00%)      | 4 / 43 (9.30%)      |
| occurrences (all)                                | 1                   | 0                   | 6                   |
| Paraesthesia                                     |                     |                     |                     |
| subjects affected / exposed                      | 4 / 33 (12.12%)     | 0 / 29 (0.00%)      | 0 / 43 (0.00%)      |
| occurrences (all)                                | 5                   | 0                   | 0                   |
| Blood and lymphatic system disorders             |                     |                     |                     |

|   |                      |                      |                     |
|---|----------------------|----------------------|---------------------|
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 33 (0.00%)<br>0  | 1 / 29 (3.45%)<br>1  | 0 / 43 (0.00%)<br>0 |
| Lymphadenitis<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 33 (0.00%)<br>0  | 0 / 29 (0.00%)<br>0  | 0 / 43 (0.00%)<br>0 |
| Lymphopenia<br>subjects affected / exposed<br>occurrences (all)                             | 6 / 33 (18.18%)<br>9 | 5 / 29 (17.24%)<br>7 | 4 / 43 (9.30%)<br>4 |
| Ear and labyrinth disorders<br>Ear pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 33 (0.00%)<br>0  | 1 / 29 (3.45%)<br>1  | 2 / 43 (4.65%)<br>2 |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)                                | 1 / 33 (3.03%)<br>1  | 0 / 29 (0.00%)<br>0  | 0 / 43 (0.00%)<br>0 |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)                                 | 4 / 33 (12.12%)<br>4 | 1 / 29 (3.45%)<br>1  | 3 / 43 (6.98%)<br>4 |
| Vertigo positional<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 33 (0.00%)<br>0  | 0 / 29 (0.00%)<br>0  | 0 / 43 (0.00%)<br>0 |
| Eye disorders<br>Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)         | 1 / 33 (3.03%)<br>1  | 0 / 29 (0.00%)<br>0  | 2 / 43 (4.65%)<br>3 |
| Eye pain<br>subjects affected / exposed<br>occurrences (all)                                | 2 / 33 (6.06%)<br>2  | 0 / 29 (0.00%)<br>0  | 0 / 43 (0.00%)<br>0 |
| Iridocyclitis<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 33 (0.00%)<br>0  | 0 / 29 (0.00%)<br>0  | 2 / 43 (4.65%)<br>5 |
| Vision blurred<br>subjects affected / exposed<br>occurrences (all)                          | 2 / 33 (6.06%)<br>2  | 0 / 29 (0.00%)<br>0  | 3 / 43 (6.98%)<br>3 |
| Gastrointestinal disorders  |                      |                      |                     |

|                                  |                |                |                 |
|----------------------------------|----------------|----------------|-----------------|
| Abdominal pain                   |                |                |                 |
| subjects affected / exposed      | 0 / 33 (0.00%) | 1 / 29 (3.45%) | 2 / 43 (4.65%)  |
| occurrences (all)                | 0              | 1              | 2               |
| Abdominal pain upper             |                |                |                 |
| subjects affected / exposed      | 0 / 33 (0.00%) | 1 / 29 (3.45%) | 3 / 43 (6.98%)  |
| occurrences (all)                | 0              | 1              | 3               |
| Aphthous ulcer                   |                |                |                 |
| subjects affected / exposed      | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 1 / 43 (2.33%)  |
| occurrences (all)                | 0              | 0              | 1               |
| Constipation                     |                |                |                 |
| subjects affected / exposed      | 1 / 33 (3.03%) | 0 / 29 (0.00%) | 0 / 43 (0.00%)  |
| occurrences (all)                | 1              | 0              | 0               |
| Diarrhoea                        |                |                |                 |
| subjects affected / exposed      | 1 / 33 (3.03%) | 2 / 29 (6.90%) | 7 / 43 (16.28%) |
| occurrences (all)                | 1              | 2              | 9               |
| Dyspepsia                        |                |                |                 |
| subjects affected / exposed      | 1 / 33 (3.03%) | 1 / 29 (3.45%) | 1 / 43 (2.33%)  |
| occurrences (all)                | 1              | 1              | 1               |
| Enteritis                        |                |                |                 |
| subjects affected / exposed      | 0 / 33 (0.00%) | 2 / 29 (6.90%) | 0 / 43 (0.00%)  |
| occurrences (all)                | 0              | 3              | 0               |
| Gastritis                        |                |                |                 |
| subjects affected / exposed      | 0 / 33 (0.00%) | 2 / 29 (6.90%) | 0 / 43 (0.00%)  |
| occurrences (all)                | 0              | 3              | 0               |
| Gastrooesophageal reflux disease |                |                |                 |
| subjects affected / exposed      | 1 / 33 (3.03%) | 0 / 29 (0.00%) | 1 / 43 (2.33%)  |
| occurrences (all)                | 1              | 0              | 2               |
| Irritable bowel syndrome         |                |                |                 |
| subjects affected / exposed      | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%)  |
| occurrences (all)                | 0              | 0              | 0               |
| Nausea                           |                |                |                 |
| subjects affected / exposed      | 1 / 33 (3.03%) | 0 / 29 (0.00%) | 0 / 43 (0.00%)  |
| occurrences (all)                | 2              | 0              | 0               |
| Toothache                        |                |                |                 |
| subjects affected / exposed      | 0 / 33 (0.00%) | 2 / 29 (6.90%) | 4 / 43 (9.30%)  |
| occurrences (all)                | 0              | 6              | 5               |

|   |                     |                      |                     |
|---|---------------------|----------------------|---------------------|
| Vomiting<br>subjects affected / exposed<br>occurrences (all)              | 1 / 33 (3.03%)<br>2 | 3 / 29 (10.34%)<br>3 | 0 / 43 (0.00%)<br>0 |
| Skin and subcutaneous tissue disorders                                    |                     |                      |                     |
| Actinic keratosis<br>subjects affected / exposed<br>occurrences (all)     | 0 / 33 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0  | 2 / 43 (4.65%)<br>2 |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)              | 2 / 33 (6.06%)<br>2 | 0 / 29 (0.00%)<br>0  | 2 / 43 (4.65%)<br>2 |
| Dermal cyst<br>subjects affected / exposed<br>occurrences (all)           | 1 / 33 (3.03%)<br>1 | 0 / 29 (0.00%)<br>0  | 0 / 43 (0.00%)<br>0 |
| Dermatitis<br>subjects affected / exposed<br>occurrences (all)            | 0 / 33 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0  | 0 / 43 (0.00%)<br>0 |
| Dermatitis allergic<br>subjects affected / exposed<br>occurrences (all)   | 0 / 33 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0  | 0 / 43 (0.00%)<br>0 |
| Dermatitis contact<br>subjects affected / exposed<br>occurrences (all)    | 1 / 33 (3.03%)<br>1 | 0 / 29 (0.00%)<br>0  | 0 / 43 (0.00%)<br>0 |
| Eczema<br>subjects affected / exposed<br>occurrences (all)                | 3 / 33 (9.09%)<br>3 | 2 / 29 (6.90%)<br>3  | 2 / 43 (4.65%)<br>2 |
| Hyperkeratosis<br>subjects affected / exposed<br>occurrences (all)        | 2 / 33 (6.06%)<br>2 | 0 / 29 (0.00%)<br>0  | 0 / 43 (0.00%)<br>0 |
| Pigmentation disorder<br>subjects affected / exposed<br>occurrences (all) | 2 / 33 (6.06%)<br>2 | 2 / 29 (6.90%)<br>2  | 1 / 43 (2.33%)<br>1 |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)              | 1 / 33 (3.03%)<br>1 | 0 / 29 (0.00%)<br>0  | 2 / 43 (4.65%)<br>2 |
| Urticaria   |                     |                      |                     |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 33 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 | 3 / 43 (6.98%)<br>3 |
| Renal and urinary disorders                      |                     |                     |                     |
| Bladder dysfunction                              |                     |                     |                     |
| subjects affected / exposed                      | 0 / 33 (0.00%)      | 0 / 29 (0.00%)      | 2 / 43 (4.65%)      |
| occurrences (all)                                | 0                   | 0                   | 2                   |
| Micturition urgency                              |                     |                     |                     |
| subjects affected / exposed                      | 2 / 33 (6.06%)      | 1 / 29 (3.45%)      | 1 / 43 (2.33%)      |
| occurrences (all)                                | 3                   | 1                   | 1                   |
| Nephrolithiasis                                  |                     |                     |                     |
| subjects affected / exposed                      | 2 / 33 (6.06%)      | 2 / 29 (6.90%)      | 0 / 43 (0.00%)      |
| occurrences (all)                                | 2                   | 2                   | 0                   |
| Urinary retention                                |                     |                     |                     |
| subjects affected / exposed                      | 1 / 33 (3.03%)      | 0 / 29 (0.00%)      | 0 / 43 (0.00%)      |
| occurrences (all)                                | 1                   | 0                   | 0                   |
| Musculoskeletal and connective tissue disorders  |                     |                     |                     |
| Arthralgia                                       |                     |                     |                     |
| subjects affected / exposed                      | 4 / 33 (12.12%)     | 3 / 29 (10.34%)     | 2 / 43 (4.65%)      |
| occurrences (all)                                | 5                   | 3                   | 2                   |
| Back pain  |                     |                     |                     |
| subjects affected / exposed                      | 6 / 33 (18.18%)     | 2 / 29 (6.90%)      | 5 / 43 (11.63%)     |
| occurrences (all)                                | 7                   | 2                   | 7                   |
| Intervertebral disc degeneration                 |                     |                     |                     |
| subjects affected / exposed                      | 0 / 33 (0.00%)      | 0 / 29 (0.00%)      | 2 / 43 (4.65%)      |
| occurrences (all)                                | 0                   | 0                   | 2                   |
| Joint swelling                                   |                     |                     |                     |
| subjects affected / exposed                      | 2 / 33 (6.06%)      | 0 / 29 (0.00%)      | 0 / 43 (0.00%)      |
| occurrences (all)                                | 2                   | 0                   | 0                   |
| Muscle spasms                                    |                     |                     |                     |
| subjects affected / exposed                      | 1 / 33 (3.03%)      | 0 / 29 (0.00%)      | 2 / 43 (4.65%)      |
| occurrences (all)                                | 1                   | 0                   | 2                   |
| Muscular weakness                                |                     |                     |                     |
| subjects affected / exposed                      | 2 / 33 (6.06%)      | 0 / 29 (0.00%)      | 2 / 43 (4.65%)      |
| occurrences (all)                                | 2                   | 0                   | 2                   |
| Musculoskeletal pain                             |                     |                     |                     |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 33 (3.03%) | 2 / 29 (6.90%) | 4 / 43 (9.30%)  |
| occurrences (all)           | 1              | 3              | 4               |
| Myalgia                     |                |                |                 |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 1 / 43 (2.33%)  |
| occurrences (all)           | 0              | 0              | 1               |
| Neck pain                   |                |                |                 |
| subjects affected / exposed | 1 / 33 (3.03%) | 2 / 29 (6.90%) | 1 / 43 (2.33%)  |
| occurrences (all)           | 1              | 4              | 1               |
| Pain in extremity           |                |                |                 |
| subjects affected / exposed | 2 / 33 (6.06%) | 1 / 29 (3.45%) | 0 / 43 (0.00%)  |
| occurrences (all)           | 2              | 1              | 0               |
| Tendonitis                  |                |                |                 |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 29 (6.90%) | 0 / 43 (0.00%)  |
| occurrences (all)           | 0              | 2              | 0               |
| Infections and infestations |                |                |                 |
| Acute sinusitis             |                |                |                 |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 29 (0.00%) | 0 / 43 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Bronchitis                  |                |                |                 |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 29 (6.90%) | 5 / 43 (11.63%) |
| occurrences (all)           | 0              | 4              | 9               |
| Conjunctivitis              |                |                |                 |
| subjects affected / exposed | 2 / 33 (6.06%) | 0 / 29 (0.00%) | 1 / 43 (2.33%)  |
| occurrences (all)           | 2              | 0              | 1               |
| Cystitis                    |                |                |                 |
| subjects affected / exposed | 3 / 33 (9.09%) | 1 / 29 (3.45%) | 2 / 43 (4.65%)  |
| occurrences (all)           | 13             | 1              | 2               |
| Fungal infection            |                |                |                 |
| subjects affected / exposed | 3 / 33 (9.09%) | 1 / 29 (3.45%) | 0 / 43 (0.00%)  |
| occurrences (all)           | 3              | 1              | 0               |
| Fungal skin infection       |                |                |                 |
| subjects affected / exposed | 2 / 33 (6.06%) | 0 / 29 (0.00%) | 0 / 43 (0.00%)  |
| occurrences (all)           | 3              | 0              | 0               |
| Gastroenteritis             |                |                |                 |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 29 (6.90%) | 1 / 43 (2.33%)  |
| occurrences (all)           | 0              | 2              | 2               |

|                             |                  |                 |                  |
|-----------------------------|------------------|-----------------|------------------|
| Gastroenteritis viral       |                  |                 |                  |
| subjects affected / exposed | 0 / 33 (0.00%)   | 0 / 29 (0.00%)  | 3 / 43 (6.98%)   |
| occurrences (all)           | 0                | 0               | 3                |
| Herpes zoster               |                  |                 |                  |
| subjects affected / exposed | 5 / 33 (15.15%)  | 0 / 29 (0.00%)  | 3 / 43 (6.98%)   |
| occurrences (all)           | 5                | 0               | 3                |
| Influenza                   |                  |                 |                  |
| subjects affected / exposed | 4 / 33 (12.12%)  | 4 / 29 (13.79%) | 5 / 43 (11.63%)  |
| occurrences (all)           | 4                | 4               | 8                |
| Nasopharyngitis             |                  |                 |                  |
| subjects affected / exposed | 10 / 33 (30.30%) | 8 / 29 (27.59%) | 17 / 43 (39.53%) |
| occurrences (all)           | 27               | 13              | 29               |
| Onychomycosis               |                  |                 |                  |
| subjects affected / exposed | 1 / 33 (3.03%)   | 1 / 29 (3.45%)  | 0 / 43 (0.00%)   |
| occurrences (all)           | 1                | 1               | 0                |
| Oral herpes                 |                  |                 |                  |
| subjects affected / exposed | 5 / 33 (15.15%)  | 0 / 29 (0.00%)  | 4 / 43 (9.30%)   |
| occurrences (all)           | 9                | 0               | 6                |
| Otitis media                |                  |                 |                  |
| subjects affected / exposed | 1 / 33 (3.03%)   | 1 / 29 (3.45%)  | 0 / 43 (0.00%)   |
| occurrences (all)           | 1                | 1               | 0                |
| Pharyngitis                 |                  |                 |                  |
| subjects affected / exposed | 1 / 33 (3.03%)   | 4 / 29 (13.79%) | 3 / 43 (6.98%)   |
| occurrences (all)           | 1                | 4               | 4                |
| Pneumonia                   |                  |                 |                  |
| subjects affected / exposed | 1 / 33 (3.03%)   | 1 / 29 (3.45%)  | 0 / 43 (0.00%)   |
| occurrences (all)           | 1                | 1               | 0                |
| Respiratory tract infection |                  |                 |                  |
| subjects affected / exposed | 0 / 33 (0.00%)   | 1 / 29 (3.45%)  | 1 / 43 (2.33%)   |
| occurrences (all)           | 0                | 1               | 1                |
| Rhinitis                    |                  |                 |                  |
| subjects affected / exposed | 3 / 33 (9.09%)   | 2 / 29 (6.90%)  | 1 / 43 (2.33%)   |
| occurrences (all)           | 3                | 2               | 1                |
| Sinusitis                   |                  |                 |                  |
| subjects affected / exposed | 3 / 33 (9.09%)   | 2 / 29 (6.90%)  | 3 / 43 (6.98%)   |
| occurrences (all)           | 4                | 2               | 5                |

|   |                       |                       |                      |
|---|-----------------------|-----------------------|----------------------|
| Subcutaneous abscess<br>subjects affected / exposed<br>occurrences (all)              | 0 / 33 (0.00%)<br>0   | 2 / 29 (6.90%)<br>2   | 0 / 43 (0.00%)<br>0  |
| Tinea versicolour<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 33 (0.00%)<br>0   | 2 / 29 (6.90%)<br>2   | 2 / 43 (4.65%)<br>2  |
| Tonsillitis<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 33 (3.03%)<br>1   | 1 / 29 (3.45%)<br>1   | 5 / 43 (11.63%)<br>5 |
| Tooth infection<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 33 (3.03%)<br>1   | 2 / 29 (6.90%)<br>4   | 1 / 43 (2.33%)<br>1  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 4 / 33 (12.12%)<br>11 | 6 / 29 (20.69%)<br>10 | 4 / 43 (9.30%)<br>7  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 6 / 33 (18.18%)<br>9  | 4 / 29 (13.79%)<br>5  | 2 / 43 (4.65%)<br>2  |
| Vaginal infection<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 33 (0.00%)<br>0   | 0 / 29 (0.00%)<br>0   | 1 / 43 (2.33%)<br>1  |
| Vulvovaginal candidiasis<br>subjects affected / exposed<br>occurrences (all)          | 0 / 33 (0.00%)<br>0   | 0 / 29 (0.00%)<br>0   | 1 / 43 (2.33%)<br>3  |
| Metabolism and nutrition disorders  |                       |                       |                      |
| Hypercholesterolaemia<br>subjects affected / exposed<br>occurrences (all)             | 2 / 33 (6.06%)<br>2   | 4 / 29 (13.79%)<br>4  | 2 / 43 (4.65%)<br>3  |
| Hypoglycaemia<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 33 (0.00%)<br>0   | 0 / 29 (0.00%)<br>0   | 0 / 43 (0.00%)<br>0  |

| <b>Non-serious adverse events</b>                                   | BAF312 0.5/2 mg   | BAF312 0.25/2 mg | All patients       |
|---|-------------------|------------------|--------------------|
| Total subjects affected by non-serious adverse events               |                   |                  |                    |
| subjects affected / exposed   | 29 / 29 (100.00%) | 42 / 50 (84.00%) | 169 / 184 (91.85%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                  |                    |



|   |                      |                      |                        |
|---|----------------------|----------------------|------------------------|
| Fibrous histiocytoma<br>subjects affected / exposed<br>occurrences (all)  | 1 / 29 (3.45%)<br>1  | 0 / 50 (0.00%)<br>0  | 5 / 184 (2.72%)<br>5   |
| Melanocytic naevus<br>subjects affected / exposed<br>occurrences (all)  | 2 / 29 (6.90%)<br>3  | 7 / 50 (14.00%)<br>8 | 18 / 184 (9.78%)<br>22 |
| Seborrhoeic keratosis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 29 (0.00%)<br>0  | 4 / 50 (8.00%)<br>4  | 7 / 184 (3.80%)<br>7   |
| Skin papilloma<br>subjects affected / exposed<br>occurrences (all)  | 2 / 29 (6.90%)<br>2  | 2 / 50 (4.00%)<br>4  | 10 / 184 (5.43%)<br>12 |
| Uterine leiomyoma<br>subjects affected / exposed<br>occurrences (all)   | 1 / 29 (3.45%)<br>1  | 0 / 50 (0.00%)<br>0  | 3 / 184 (1.63%)<br>3   |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)                                  | 3 / 29 (10.34%)<br>3 | 8 / 50 (16.00%)<br>8 | 16 / 184 (8.70%)<br>17 |
| General disorders and administration<br>site conditions<br>Asthenia<br>subjects affected / exposed<br>occurrences (all) | 0 / 29 (0.00%)<br>0  | 1 / 50 (2.00%)<br>2  | 4 / 184 (2.17%)<br>5   |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)   | 2 / 29 (6.90%)<br>2  | 6 / 50 (12.00%)<br>6 | 18 / 184 (9.78%)<br>20 |
| Gait disturbance<br>subjects affected / exposed<br>occurrences (all)  | 1 / 29 (3.45%)<br>1  | 0 / 50 (0.00%)<br>0  | 4 / 184 (2.17%)<br>4   |
| Influenza like illness<br>subjects affected / exposed<br>occurrences (all)  | 1 / 29 (3.45%)<br>2  | 1 / 50 (2.00%)<br>1  | 5 / 184 (2.72%)<br>6   |
| Non-cardiac chest pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 29 (0.00%)<br>0  | 2 / 50 (4.00%)<br>3  | 6 / 184 (3.26%)<br>7   |
| Oedema peripheral   |                      |                      |                        |

|   |                 |                 |                  |
|---|-----------------|-----------------|------------------|
| subjects affected / exposed                     | 1 / 29 (3.45%)  | 0 / 50 (0.00%)  | 3 / 184 (1.63%)  |
| occurrences (all)                               | 1               | 0               | 3                |
| Pyrexia   |                 |                 |                  |
| subjects affected / exposed                     | 3 / 29 (10.34%) | 5 / 50 (10.00%) | 15 / 184 (8.15%) |
| occurrences (all)                               | 5               | 6               | 20               |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                  |
| Catarrh   |                 |                 |                  |
| subjects affected / exposed                     | 2 / 29 (6.90%)  | 0 / 50 (0.00%)  | 4 / 184 (2.17%)  |
| occurrences (all)                               | 5               | 0               | 8                |
| Cough   |                 |                 |                  |
| subjects affected / exposed                     | 4 / 29 (13.79%) | 2 / 50 (4.00%)  | 15 / 184 (8.15%) |
| occurrences (all)                               | 9               | 2               | 23               |
| Dyspnoea  |                 |                 |                  |
| subjects affected / exposed                     | 0 / 29 (0.00%)  | 1 / 50 (2.00%)  | 3 / 184 (1.63%)  |
| occurrences (all)                               | 0               | 1               | 3                |
| Epistaxis                                       |                 |                 |                  |
| subjects affected / exposed                     | 2 / 29 (6.90%)  | 0 / 50 (0.00%)  | 2 / 184 (1.09%)  |
| occurrences (all)                               | 2               | 0               | 2                |
| Oropharyngeal pain                              |                 |                 |                  |
| subjects affected / exposed                     | 0 / 29 (0.00%)  | 3 / 50 (6.00%)  | 10 / 184 (5.43%) |
| occurrences (all)                               | 0               | 4               | 11               |
| Rhinitis allergic                               |                 |                 |                  |
| subjects affected / exposed                     | 0 / 29 (0.00%)  | 2 / 50 (4.00%)  | 4 / 184 (2.17%)  |
| occurrences (all)                               | 0               | 2               | 6                |
| Wheezing  |                 |                 |                  |
| subjects affected / exposed                     | 0 / 29 (0.00%)  | 2 / 50 (4.00%)  | 2 / 184 (1.09%)  |
| occurrences (all)                               | 0               | 2               | 2                |
| Psychiatric disorders                           |                 |                 |                  |
| Anxiety   |                 |                 |                  |
| subjects affected / exposed                     | 0 / 29 (0.00%)  | 4 / 50 (8.00%)  | 9 / 184 (4.89%)  |
| occurrences (all)                               | 0               | 4               | 10               |
| Depression                                      |                 |                 |                  |
| subjects affected / exposed                     | 3 / 29 (10.34%) | 7 / 50 (14.00%) | 18 / 184 (9.78%) |
| occurrences (all)                               | 3               | 11              | 22               |
| Insomnia  |                 |                 |                  |

|   |                      |                      |                         |
|---|----------------------|----------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)  | 3 / 29 (10.34%)<br>3 | 6 / 50 (12.00%)<br>8 | 20 / 184 (10.87%)<br>23 |
| Sleep disorder<br>subjects affected / exposed<br>occurrences (all)                      | 2 / 29 (6.90%)<br>4  | 0 / 50 (0.00%)<br>0  | 3 / 184 (1.63%)<br>5    |
| Investigations  |                      |                      |                         |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)  | 2 / 29 (6.90%)<br>3  | 2 / 50 (4.00%)<br>2  | 15 / 184 (8.15%)<br>19  |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)           | 0 / 29 (0.00%)<br>0  | 2 / 50 (4.00%)<br>3  | 2 / 184 (1.09%)<br>3    |
| Blood cholesterol increased<br>subjects affected / exposed<br>occurrences (all)         | 2 / 29 (6.90%)<br>2  | 1 / 50 (2.00%)<br>2  | 4 / 184 (2.17%)<br>5    |
| C-reactive protein increased<br>subjects affected / exposed<br>occurrences (all)        | 0 / 29 (0.00%)<br>0  | 3 / 50 (6.00%)<br>4  | 5 / 184 (2.72%)<br>6    |
| Gamma-glutamyltransferase increased<br>subjects affected / exposed<br>occurrences (all) | 3 / 29 (10.34%)<br>3 | 2 / 50 (4.00%)<br>2  | 13 / 184 (7.07%)<br>15  |
| Hepatic enzyme increased<br>subjects affected / exposed<br>occurrences (all)            | 0 / 29 (0.00%)<br>0  | 1 / 50 (2.00%)<br>1  | 5 / 184 (2.72%)<br>5    |
| Lymphocyte count decreased<br>subjects affected / exposed<br>occurrences (all)          | 2 / 29 (6.90%)<br>3  | 3 / 50 (6.00%)<br>6  | 15 / 184 (8.15%)<br>26  |
| Injury, poisoning and procedural complications  |                      |                      |                         |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                           | 3 / 29 (10.34%)<br>5 | 1 / 50 (2.00%)<br>1  | 8 / 184 (4.35%)<br>14   |
| Fall<br>subjects affected / exposed<br>occurrences (all)                                | 2 / 29 (6.90%)<br>3  | 1 / 50 (2.00%)<br>8  | 9 / 184 (4.89%)<br>18   |
| Joint injury  |                      |                      |                         |

|   |                       |                        |                         |
|---|-----------------------|------------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)                      | 0 / 29 (0.00%)<br>0   | 0 / 50 (0.00%)<br>0    | 3 / 184 (1.63%)<br>3    |
| Ligament sprain<br>subjects affected / exposed<br>occurrences (all)   | 2 / 29 (6.90%)<br>2   | 1 / 50 (2.00%)<br>1    | 7 / 184 (3.80%)<br>7    |
| Limb injury<br>subjects affected / exposed<br>occurrences (all)       | 1 / 29 (3.45%)<br>1   | 2 / 50 (4.00%)<br>2    | 3 / 184 (1.63%)<br>3    |
| Cardiac disorders   |                       |                        |                         |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)      | 0 / 29 (0.00%)<br>0   | 1 / 50 (2.00%)<br>1    | 3 / 184 (1.63%)<br>3    |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)       | 0 / 29 (0.00%)<br>0   | 2 / 50 (4.00%)<br>3    | 3 / 184 (1.63%)<br>4    |
| Nervous system disorders  |                       |                        |                         |
| Burning sensation<br>subjects affected / exposed<br>occurrences (all) | 0 / 29 (0.00%)<br>0   | 2 / 50 (4.00%)<br>2    | 3 / 184 (1.63%)<br>3    |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)         | 1 / 29 (3.45%)<br>1   | 4 / 50 (8.00%)<br>4    | 8 / 184 (4.35%)<br>8    |
| Headache<br>subjects affected / exposed<br>occurrences (all)          | 4 / 29 (13.79%)<br>12 | 10 / 50 (20.00%)<br>14 | 36 / 184 (19.57%)<br>56 |
| Hypoaesthesia<br>subjects affected / exposed<br>occurrences (all)     | 1 / 29 (3.45%)<br>2   | 2 / 50 (4.00%)<br>2    | 4 / 184 (2.17%)<br>7    |
| Migraine<br>subjects affected / exposed<br>occurrences (all)          | 1 / 29 (3.45%)<br>1   | 0 / 50 (0.00%)<br>0    | 6 / 184 (3.26%)<br>6    |
| Muscle spasticity<br>subjects affected / exposed<br>occurrences (all) | 3 / 29 (10.34%)<br>3  | 0 / 50 (0.00%)<br>0    | 5 / 184 (2.72%)<br>5    |
| Neuralgia   |                       |                        |                         |

|  |                      |                      |                         |
|--|----------------------|----------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)                       | 0 / 29 (0.00%)<br>0  | 0 / 50 (0.00%)<br>0  | 5 / 184 (2.72%)<br>7    |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)       | 2 / 29 (6.90%)<br>3  | 3 / 50 (6.00%)<br>3  | 9 / 184 (4.89%)<br>11   |
| Blood and lymphatic system disorders                                   |                      |                      |                         |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)         | 2 / 29 (6.90%)<br>2  | 0 / 50 (0.00%)<br>0  | 3 / 184 (1.63%)<br>3    |
| Lymphadenitis<br>subjects affected / exposed<br>occurrences (all)      | 0 / 29 (0.00%)<br>0  | 2 / 50 (4.00%)<br>2  | 2 / 184 (1.09%)<br>2    |
| Lymphopenia<br>subjects affected / exposed<br>occurrences (all)        | 6 / 29 (20.69%)<br>9 | 3 / 50 (6.00%)<br>3  | 24 / 184 (13.04%)<br>32 |
| Ear and labyrinth disorders  |                      |                      |                         |
| Ear pain<br>subjects affected / exposed<br>occurrences (all)           | 0 / 29 (0.00%)<br>0  | 1 / 50 (2.00%)<br>1  | 4 / 184 (2.17%)<br>4    |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)           | 0 / 29 (0.00%)<br>0  | 2 / 50 (4.00%)<br>2  | 3 / 184 (1.63%)<br>3    |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)            | 2 / 29 (6.90%)<br>2  | 6 / 50 (12.00%)<br>6 | 16 / 184 (8.70%)<br>17  |
| Vertigo positional<br>subjects affected / exposed<br>occurrences (all) | 2 / 29 (6.90%)<br>2  | 1 / 50 (2.00%)<br>1  | 3 / 184 (1.63%)<br>3    |
| Eye disorders  |                      |                      |                         |
| Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)     | 1 / 29 (3.45%)<br>1  | 1 / 50 (2.00%)<br>1  | 5 / 184 (2.72%)<br>6    |
| Eye pain<br>subjects affected / exposed<br>occurrences (all)           | 1 / 29 (3.45%)<br>1  | 0 / 50 (0.00%)<br>0  | 3 / 184 (1.63%)<br>3    |
| Iridocyclitis  |                      |                      |                         |

|                                  |                 |                 |                   |
|----------------------------------|-----------------|-----------------|-------------------|
| subjects affected / exposed      | 0 / 29 (0.00%)  | 0 / 50 (0.00%)  | 2 / 184 (1.09%)   |
| occurrences (all)                | 0               | 0               | 5                 |
| Vision blurred                   |                 |                 |                   |
| subjects affected / exposed      | 0 / 29 (0.00%)  | 0 / 50 (0.00%)  | 5 / 184 (2.72%)   |
| occurrences (all)                | 0               | 0               | 5                 |
| Gastrointestinal disorders       |                 |                 |                   |
| Abdominal pain                   |                 |                 |                   |
| subjects affected / exposed      | 1 / 29 (3.45%)  | 3 / 50 (6.00%)  | 7 / 184 (3.80%)   |
| occurrences (all)                | 2               | 3               | 8                 |
| Abdominal pain upper             |                 |                 |                   |
| subjects affected / exposed      | 5 / 29 (17.24%) | 3 / 50 (6.00%)  | 12 / 184 (6.52%)  |
| occurrences (all)                | 5               | 3               | 12                |
| Aphthous ulcer                   |                 |                 |                   |
| subjects affected / exposed      | 2 / 29 (6.90%)  | 0 / 50 (0.00%)  | 3 / 184 (1.63%)   |
| occurrences (all)                | 3               | 0               | 4                 |
| Constipation                     |                 |                 |                   |
| subjects affected / exposed      | 0 / 29 (0.00%)  | 3 / 50 (6.00%)  | 4 / 184 (2.17%)   |
| occurrences (all)                | 0               | 3               | 4                 |
| Diarrhoea                        |                 |                 |                   |
| subjects affected / exposed      | 3 / 29 (10.34%) | 6 / 50 (12.00%) | 19 / 184 (10.33%) |
| occurrences (all)                | 3               | 7               | 22                |
| Dyspepsia                        |                 |                 |                   |
| subjects affected / exposed      | 0 / 29 (0.00%)  | 2 / 50 (4.00%)  | 5 / 184 (2.72%)   |
| occurrences (all)                | 0               | 2               | 5                 |
| Enteritis                        |                 |                 |                   |
| subjects affected / exposed      | 0 / 29 (0.00%)  | 0 / 50 (0.00%)  | 2 / 184 (1.09%)   |
| occurrences (all)                | 0               | 0               | 3                 |
| Gastritis                        |                 |                 |                   |
| subjects affected / exposed      | 1 / 29 (3.45%)  | 0 / 50 (0.00%)  | 3 / 184 (1.63%)   |
| occurrences (all)                | 2               | 0               | 5                 |
| Gastrooesophageal reflux disease |                 |                 |                   |
| subjects affected / exposed      | 3 / 29 (10.34%) | 1 / 50 (2.00%)  | 6 / 184 (3.26%)   |
| occurrences (all)                | 3               | 1               | 7                 |
| Irritable bowel syndrome         |                 |                 |                   |
| subjects affected / exposed      | 2 / 29 (6.90%)  | 0 / 50 (0.00%)  | 2 / 184 (1.09%)   |
| occurrences (all)                | 2               | 0               | 2                 |

|  |                 |                |                  |
|--|-----------------|----------------|------------------|
| Nausea                                 |                 |                |                  |
| subjects affected / exposed            | 3 / 29 (10.34%) | 4 / 50 (8.00%) | 8 / 184 (4.35%)  |
| occurrences (all)                      | 5               | 6              | 13               |
| Toothache                              |                 |                |                  |
| subjects affected / exposed            | 1 / 29 (3.45%)  | 4 / 50 (8.00%) | 11 / 184 (5.98%) |
| occurrences (all)                      | 1               | 6              | 18               |
| Vomiting                               |                 |                |                  |
| subjects affected / exposed            | 0 / 29 (0.00%)  | 3 / 50 (6.00%) | 7 / 184 (3.80%)  |
| occurrences (all)                      | 0               | 3              | 8                |
| Skin and subcutaneous tissue disorders |                 |                |                  |
| Actinic keratosis                      |                 |                |                  |
| subjects affected / exposed            | 0 / 29 (0.00%)  | 0 / 50 (0.00%) | 2 / 184 (1.09%)  |
| occurrences (all)                      | 0               | 0              | 2                |
| Alopecia                               |                 |                |                  |
| subjects affected / exposed            | 0 / 29 (0.00%)  | 1 / 50 (2.00%) | 5 / 184 (2.72%)  |
| occurrences (all)                      | 0               | 1              | 5                |
| Dermal cyst                            |                 |                |                  |
| subjects affected / exposed            | 2 / 29 (6.90%)  | 0 / 50 (0.00%) | 3 / 184 (1.63%)  |
| occurrences (all)                      | 2               | 0              | 3                |
| Dermatitis                             |                 |                |                  |
| subjects affected / exposed            | 0 / 29 (0.00%)  | 2 / 50 (4.00%) | 2 / 184 (1.09%)  |
| occurrences (all)                      | 0               | 2              | 2                |
| Dermatitis allergic                    |                 |                |                  |
| subjects affected / exposed            | 2 / 29 (6.90%)  | 2 / 50 (4.00%) | 4 / 184 (2.17%)  |
| occurrences (all)                      | 2               | 2              | 4                |
| Dermatitis contact                     |                 |                |                  |
| subjects affected / exposed            | 2 / 29 (6.90%)  | 0 / 50 (0.00%) | 3 / 184 (1.63%)  |
| occurrences (all)                      | 2               | 0              | 3                |
| Eczema                                 |                 |                |                  |
| subjects affected / exposed            | 0 / 29 (0.00%)  | 1 / 50 (2.00%) | 8 / 184 (4.35%)  |
| occurrences (all)                      | 0               | 1              | 9                |
| Hyperkeratosis                         |                 |                |                  |
| subjects affected / exposed            | 0 / 29 (0.00%)  | 0 / 50 (0.00%) | 2 / 184 (1.09%)  |
| occurrences (all)                      | 0               | 0              | 2                |
| Pigmentation disorder                  |                 |                |                  |

|   |                      |                     |                         |
|---|----------------------|---------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 29 (0.00%)<br>0  | 0 / 50 (0.00%)<br>0 | 5 / 184 (2.72%)<br>5    |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)  | 1 / 29 (3.45%)<br>1  | 3 / 50 (6.00%)<br>4 | 7 / 184 (3.80%)<br>8    |
| Urticaria<br>subjects affected / exposed<br>occurrences (all)   | 1 / 29 (3.45%)<br>1  | 1 / 50 (2.00%)<br>1 | 5 / 184 (2.72%)<br>5    |
| Renal and urinary disorders<br>Bladder dysfunction<br>subjects affected / exposed<br>occurrences (all)            | 0 / 29 (0.00%)<br>0  | 0 / 50 (0.00%)<br>0 | 2 / 184 (1.09%)<br>2    |
| Micturition urgency<br>subjects affected / exposed<br>occurrences (all)   | 0 / 29 (0.00%)<br>0  | 1 / 50 (2.00%)<br>1 | 5 / 184 (2.72%)<br>6    |
| Nephrolithiasis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 29 (3.45%)<br>1  | 0 / 50 (0.00%)<br>0 | 5 / 184 (2.72%)<br>5    |
| Urinary retention<br>subjects affected / exposed<br>occurrences (all)   | 2 / 29 (6.90%)<br>3  | 0 / 50 (0.00%)<br>0 | 3 / 184 (1.63%)<br>4    |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 2 / 29 (6.90%)<br>2  | 3 / 50 (6.00%)<br>3 | 14 / 184 (7.61%)<br>15  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 3 / 29 (10.34%)<br>3 | 3 / 50 (6.00%)<br>3 | 19 / 184 (10.33%)<br>22 |
| Intervertebral disc degeneration<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 29 (0.00%)<br>0  | 0 / 50 (0.00%)<br>0 | 2 / 184 (1.09%)<br>2    |
| Joint swelling<br>subjects affected / exposed<br>occurrences (all)  | 0 / 29 (0.00%)<br>0  | 1 / 50 (2.00%)<br>1 | 3 / 184 (1.63%)<br>3    |
| Muscle spasms   |                      |                     |                         |



|                             |                 |                 |                  |
|-----------------------------|-----------------|-----------------|------------------|
| subjects affected / exposed | 1 / 29 (3.45%)  | 1 / 50 (2.00%)  | 5 / 184 (2.72%)  |
| occurrences (all)           | 1               | 1               | 5                |
| Muscular weakness           |                 |                 |                  |
| subjects affected / exposed | 0 / 29 (0.00%)  | 0 / 50 (0.00%)  | 4 / 184 (2.17%)  |
| occurrences (all)           | 0               | 0               | 4                |
| Musculoskeletal pain        |                 |                 |                  |
| subjects affected / exposed | 0 / 29 (0.00%)  | 2 / 50 (4.00%)  | 9 / 184 (4.89%)  |
| occurrences (all)           | 0               | 2               | 10               |
| Myalgia                     |                 |                 |                  |
| subjects affected / exposed | 0 / 29 (0.00%)  | 3 / 50 (6.00%)  | 4 / 184 (2.17%)  |
| occurrences (all)           | 0               | 4               | 5                |
| Neck pain                   |                 |                 |                  |
| subjects affected / exposed | 0 / 29 (0.00%)  | 2 / 50 (4.00%)  | 6 / 184 (3.26%)  |
| occurrences (all)           | 0               | 2               | 8                |
| Pain in extremity           |                 |                 |                  |
| subjects affected / exposed | 4 / 29 (13.79%) | 5 / 50 (10.00%) | 12 / 184 (6.52%) |
| occurrences (all)           | 4               | 9               | 16               |
| Tendonitis                  |                 |                 |                  |
| subjects affected / exposed | 2 / 29 (6.90%)  | 2 / 50 (4.00%)  | 6 / 184 (3.26%)  |
| occurrences (all)           | 2               | 2               | 6                |
| Infections and infestations |                 |                 |                  |
| Acute sinusitis             |                 |                 |                  |
| subjects affected / exposed | 0 / 29 (0.00%)  | 3 / 50 (6.00%)  | 3 / 184 (1.63%)  |
| occurrences (all)           | 0               | 3               | 3                |
| Bronchitis                  |                 |                 |                  |
| subjects affected / exposed | 3 / 29 (10.34%) | 6 / 50 (12.00%) | 16 / 184 (8.70%) |
| occurrences (all)           | 3               | 7               | 23               |
| Conjunctivitis              |                 |                 |                  |
| subjects affected / exposed | 0 / 29 (0.00%)  | 0 / 50 (0.00%)  | 3 / 184 (1.63%)  |
| occurrences (all)           | 0               | 0               | 3                |
| Cystitis                    |                 |                 |                  |
| subjects affected / exposed | 1 / 29 (3.45%)  | 1 / 50 (2.00%)  | 8 / 184 (4.35%)  |
| occurrences (all)           | 1               | 4               | 21               |
| Fungal infection            |                 |                 |                  |
| subjects affected / exposed | 1 / 29 (3.45%)  | 1 / 50 (2.00%)  | 6 / 184 (3.26%)  |
| occurrences (all)           | 1               | 3               | 8                |

|                             |                  |                  |                   |
|-----------------------------|------------------|------------------|-------------------|
| Fungal skin infection       |                  |                  |                   |
| subjects affected / exposed | 0 / 29 (0.00%)   | 0 / 50 (0.00%)   | 2 / 184 (1.09%)   |
| occurrences (all)           | 0                | 0                | 3                 |
| Gastroenteritis             |                  |                  |                   |
| subjects affected / exposed | 3 / 29 (10.34%)  | 4 / 50 (8.00%)   | 10 / 184 (5.43%)  |
| occurrences (all)           | 4                | 5                | 13                |
| Gastroenteritis viral       |                  |                  |                   |
| subjects affected / exposed | 0 / 29 (0.00%)   | 2 / 50 (4.00%)   | 5 / 184 (2.72%)   |
| occurrences (all)           | 0                | 2                | 5                 |
| Herpes zoster               |                  |                  |                   |
| subjects affected / exposed | 2 / 29 (6.90%)   | 0 / 50 (0.00%)   | 10 / 184 (5.43%)  |
| occurrences (all)           | 2                | 0                | 10                |
| Influenza                   |                  |                  |                   |
| subjects affected / exposed | 7 / 29 (24.14%)  | 7 / 50 (14.00%)  | 27 / 184 (14.67%) |
| occurrences (all)           | 9                | 11               | 36                |
| Nasopharyngitis             |                  |                  |                   |
| subjects affected / exposed | 11 / 29 (37.93%) | 18 / 50 (36.00%) | 64 / 184 (34.78%) |
| occurrences (all)           | 27               | 49               | 145               |
| Onychomycosis               |                  |                  |                   |
| subjects affected / exposed | 0 / 29 (0.00%)   | 3 / 50 (6.00%)   | 5 / 184 (2.72%)   |
| occurrences (all)           | 0                | 3                | 5                 |
| Oral herpes                 |                  |                  |                   |
| subjects affected / exposed | 2 / 29 (6.90%)   | 4 / 50 (8.00%)   | 15 / 184 (8.15%)  |
| occurrences (all)           | 19               | 11               | 45                |
| Otitis media                |                  |                  |                   |
| subjects affected / exposed | 0 / 29 (0.00%)   | 3 / 50 (6.00%)   | 5 / 184 (2.72%)   |
| occurrences (all)           | 0                | 3                | 5                 |
| Pharyngitis                 |                  |                  |                   |
| subjects affected / exposed | 6 / 29 (20.69%)  | 3 / 50 (6.00%)   | 17 / 184 (9.24%)  |
| occurrences (all)           | 6                | 3                | 18                |
| Pneumonia                   |                  |                  |                   |
| subjects affected / exposed | 0 / 29 (0.00%)   | 2 / 50 (4.00%)   | 4 / 184 (2.17%)   |
| occurrences (all)           | 0                | 2                | 4                 |
| Respiratory tract infection |                  |                  |                   |
| subjects affected / exposed | 1 / 29 (3.45%)   | 2 / 50 (4.00%)   | 5 / 184 (2.72%)   |
| occurrences (all)           | 1                | 4                | 7                 |

|                                    |                 |                 |                   |
|------------------------------------|-----------------|-----------------|-------------------|
| Rhinitis                           |                 |                 |                   |
| subjects affected / exposed        | 0 / 29 (0.00%)  | 1 / 50 (2.00%)  | 7 / 184 (3.80%)   |
| occurrences (all)                  | 0               | 6               | 12                |
| Sinusitis                          |                 |                 |                   |
| subjects affected / exposed        | 5 / 29 (17.24%) | 5 / 50 (10.00%) | 18 / 184 (9.78%)  |
| occurrences (all)                  | 8               | 6               | 25                |
| Subcutaneous abscess               |                 |                 |                   |
| subjects affected / exposed        | 0 / 29 (0.00%)  | 0 / 50 (0.00%)  | 2 / 184 (1.09%)   |
| occurrences (all)                  | 0               | 0               | 2                 |
| Tinea versicolour                  |                 |                 |                   |
| subjects affected / exposed        | 0 / 29 (0.00%)  | 1 / 50 (2.00%)  | 5 / 184 (2.72%)   |
| occurrences (all)                  | 0               | 1               | 5                 |
| Tonsillitis                        |                 |                 |                   |
| subjects affected / exposed        | 2 / 29 (6.90%)  | 1 / 50 (2.00%)  | 10 / 184 (5.43%)  |
| occurrences (all)                  | 2               | 1               | 10                |
| Tooth infection                    |                 |                 |                   |
| subjects affected / exposed        | 1 / 29 (3.45%)  | 0 / 50 (0.00%)  | 5 / 184 (2.72%)   |
| occurrences (all)                  | 2               | 0               | 8                 |
| Upper respiratory tract infection  |                 |                 |                   |
| subjects affected / exposed        | 7 / 29 (24.14%) | 9 / 50 (18.00%) | 30 / 184 (16.30%) |
| occurrences (all)                  | 14              | 11              | 53                |
| Urinary tract infection            |                 |                 |                   |
| subjects affected / exposed        | 4 / 29 (13.79%) | 4 / 50 (8.00%)  | 20 / 184 (10.87%) |
| occurrences (all)                  | 7               | 12              | 35                |
| Vaginal infection                  |                 |                 |                   |
| subjects affected / exposed        | 2 / 29 (6.90%)  | 2 / 50 (4.00%)  | 5 / 184 (2.72%)   |
| occurrences (all)                  | 2               | 2               | 5                 |
| Vulvovaginal candidiasis           |                 |                 |                   |
| subjects affected / exposed        | 1 / 29 (3.45%)  | 2 / 50 (4.00%)  | 4 / 184 (2.17%)   |
| occurrences (all)                  | 1               | 2               | 6                 |
| Metabolism and nutrition disorders |                 |                 |                   |
| Hypercholesterolaemia              |                 |                 |                   |
| subjects affected / exposed        | 1 / 29 (3.45%)  | 3 / 50 (6.00%)  | 12 / 184 (6.52%)  |
| occurrences (all)                  | 1               | 10              | 20                |
| Hypoglycaemia                      |                 |                 |                   |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 50 (4.00%) | 2 / 184 (1.09%) |
| occurrences (all)           | 0              | 2              | 2               |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 07 May 2010      | The amendment was to introduce measures to mitigate observed bradyarrhythmic effects by means of dose titration and an enhanced monitoring to identify and to manage patients at risk. Further, the amendment introduced the need for re-screening of patients who had study drug interruptions of more than 4 weeks between completing the Core Study and starting the participation in the Extension Study. Corresponding changes were made to the study design and dose titration content as well as in-house monitoring and cardiac exclusion criteria. |
| 05 November 2010 | Introduced an interim analysis to evaluate the safety of the dose-titration scheme used during the first 10 days of the study. Data of interest included heart rate, ECG parameters, and AEs.   |
| 13 June 2012     | Incorporated the OL Phase into the study design and changed siponimod dosing from 5 separate fixed-dose groups to a 2 mg/day fixed dose. Study was extended from 2 years up to 5 years  |
| 19 March 2014    | Key changes were adding an abbreviated visit schedule option for patients who stopped taking study medication and continued in the study, allowed concomitant treatment with beta blockers, provided updated details on potent inhibitors/inducers of CYP2C9 and further extended the study duration (beyond 5 years)   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This study was prematurely discontinued after approximately 5 years. The decision to prematurely discontinue the study was not taken due to safety-related concerns, but a decision to focus the development of siponimod in MS on a different population

Notes: