

**Clinical trial results:****Efficacy and safety of Eslicarbazepine Acetate (BIA 2 093) as adjunctive therapy for refractory partial seizures in children: a double-blind, randomised, placebo-controlled, parallel-group, multicentre clinical trial****Summary**

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2007-001887-55                |
| Trial protocol           | PT HU CZ AT FR SK IT ES GB DE |
| Global end of trial date |                               |

**Results information**

|                                   |  |
|-----------------------------------|--|
| Result version number             | v2   |
| This version publication date     | 22 July 2016   |
| First version publication date    | 07 August 2015   |
| Version creation reason           |  |
| Summary attachment (see zip file) | BIA-2093-305_Synopsis_part I-II (BIA-2093-305_Synopsis_part I-II.pdf)<br>BIA-2093-305_Synopsis_part III-V (BIA-2093-305_Synopsis_part III-V.pdf) |

**Trial information****Trial identification**

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | BIA-2093-305 |
|-----------------------|--------------|

**Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00988156 |
| WHO universal trial number (UTN)   | -           |

Notes:

**Sponsors**

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | BIAL - Portela & CA, S.A.   |
| Sponsor organisation address | À Av. Siderurgia Nacional, Coronado, Portugal, 4745-457                               |
| Public contact               | André Garrido, BIAL - Portela & Cª, S.A., 00351 229866100, andre.garrido@bial.com     |
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Notes:

**Paediatric regulatory details**

|  |                      |
|--|----------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                  |
| EMA paediatric investigation plan number(s)                          | EMEA-000696-PIP02-10 |
| 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? | Yes                  |

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Interim          |
| Date of interim/final analysis                       | 03 November 2014 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 14 August 2012   |
| Global end of trial reached?                         | No               |

Notes:

## General information about the trial

Main objective of the trial:

Primary: The primary objective of the study is to assess the efficacy of Eslicarbazepine Acetate as adjunctive therapy in children and adolescents with refractory partial seizures.

The primary analysis variables for the assessment of efficacy will be:

1. the responder rate, defined as the proportion of patients with at least a 50% decrease in the standardised seizure frequency
2. the relative reduction in the standardised seizure frequency

Protection of trial subjects:

The trial was conducted in accordance with the International Conference on Harmonisation (ICH), Good Clinical Practices (GCP), Good Manufacturing Practice (GMP), the ethical principles of the Declaration of Helsinki and with applicable local regulations. This trial was conducted by qualified persons who respected the rights and welfare of the subjects and after the review and approval of the protocol by an EC. Adverse events were collected throughout the trial and subject was followed by 4 weeks after last treatment visit in the double blind phase and 4 weeks after last treatment visit in the open blind phase.

Background therapy:

Concomitant AED therapy (1 or 2 AEDs).

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 07 December 2007 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                           |
|--------------------------------------|---------------------------|
| Country: Number of subjects enrolled | Austria: 3                |
| Country: Number of subjects enrolled | Bosnia and Herzegovina: 4 |
| Country: Number of subjects enrolled | Czech Republic: 31        |
| Country: Number of subjects enrolled | Germany: 1                |
| Country: Number of subjects enrolled | Spain: 4                  |
| Country: Number of subjects enrolled | France: 9                 |
| Country: Number of subjects enrolled | United Kingdom: 9         |
| Country: Number of subjects enrolled | Croatia: 4                |
| Country: Number of subjects enrolled | Hungary: 38               |
| Country: Number of subjects enrolled | Italy: 12                 |
| Country: Number of subjects enrolled | Malaysia: 3               |
| Country: Number of subjects enrolled | Philippines: 17           |
| Country: Number of subjects enrolled | Poland: 22                |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Portugal: 8            |
| Country: Number of subjects enrolled | Romania: 4             |
| Country: Number of subjects enrolled | Russian Federation: 20 |
| Country: Number of subjects enrolled | Serbia: 37             |
| Country: Number of subjects enrolled | Slovakia: 15           |
| Country: Number of subjects enrolled | Ukraine: 63            |
| Worldwide total number of subjects   | 304                    |
| EEA total number of subjects         | 160                    |

Notes:

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### **Subjects enrolled per age group**

|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 207 |
| Adolescents (12-17 years)                 | 96  |
| Adults (18-64 years)                      | 1   |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

The patient recruitment period will last approximately 66 months. The actual overall study duration or patient recruitment period may vary.

### Pre-assignment

Screening details:

Subjects who met all the inclusion criteria and none of the exclusion criteria. 370 subjects were enrolled to the trial and 66 subjects were screening failures including 5 IMP recalls and 41 randomised subjects were IMP recall.

### Pre-assignment period milestones

|                              |                    |
|------------------------------|--------------------|
| Number of subjects started   | 370 <sup>[1]</sup> |
| Number of subjects completed | 263                |

### Pre-assignment subject non-completion reasons

|                            |   |
|----------------------------|---|
| Reason: Number of subjects | Adverse event, non-fatal: 2                       |
| Reason: Number of subjects | Consent withdrawn by subject: 3                   |
| Reason: Number of subjects | Physician decision: 1                             |
| Reason: Number of subjects | Ineligibility: 44                                 |
| Reason: Number of subjects | Treatment with > 2 conc. AEDs at the same time: 5 |
| Reason: Number of subjects | IMP recall: 46                                    |
| Reason: Number of subjects | Sponsor decision: 6                               |

Notes:

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

Justification: The number of subjects reported to have started the pre-assignment period is the number of enrolled subjects; The worldwide number is number of treated subjects.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | PART I: DOUBLE-BLIND TREATMENT |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Double blind                   |
| Roles blinded                | Subject, Investigator, Carer   |

### Arms

|                              |                  |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes              |
| Arm title                    | Part I - Placebo |

Arm description:

Patients aged 2–6 years will receive the study treatment as 50 mg/mL placebo oral suspension. Patients aged 7 or over will receive the study treatment in the form of 200 mg placebo tablets. The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily. Subjects without IMP recall.

|  |                         |
|--|-------------------------|
| Arm type                               | Placebo                 |
| Investigational medicinal product name | Placebo                 |
| Investigational medicinal product code |                         |
| Other name                             |                         |
| Pharmaceutical forms                   | Tablet, Oral suspension |
| Routes of administration               | Oral use                |

**Dosage and administration details:**

The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily.

**Titration period:**

First 2 weeks: 10 mg/kg/day;

Next 4 weeks: 20 mg/kg/day (maximum 1200 mg/day) (if no AE occurred), 10 mg/kg/day (if AE occurred);

**Maintenance period:**

Next 12 weeks: 20 mg/kg/day (if acceptable tolerability), 30 mg/kg/day (maximum 1200 mg/day) (if unsatisfactory response), 10 mg/kg/day (if during the previous period will receive this dose)

**Tapering-off \follow-up period:**

After the 12-week maintenance period, the study treatment will be tapered off in 10 mg/kg/day steps every 2 weeks, followed by a 4 week observational follow-up period.

|                  |              |
|------------------|--------------|
| <b>Arm title</b> | Part I - ESL |
|------------------|--------------|

**Arm description:**

Patients aged 2–6 years will receive the study treatment as 50 mg/mL Eslicarbazepine Acetate oral suspension. Patients aged 7 or over will receive the study treatment in the form of 200 mg Eslicarbazepine Acetate tablets. The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily. Subjects without IMP recall.

|  |                         |
|--|-------------------------|
| Arm type                               | Active comparator       |
| Investigational medicinal product name | Eslicarbazepine acetate |
| Investigational medicinal product code | BIA 2093                |
| Other name                             | Zebinix                 |
| Pharmaceutical forms                   | Tablet, Oral suspension |
| Routes of administration               | Oral use                |

**Dosage and administration details:**

The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily.

**Titration period:**

First 2 weeks: 10 mg/kg/day;

Next 4 weeks: 20 mg/kg/day (maximum 1200 mg/day) (if no AE occurred), 10 mg/kg/day (if AE occurred);

**Maintenance period:**

Next 12 weeks: 20 mg/kg/day (if acceptable tolerability), 30 mg/kg/day (maximum 1200 mg/day) (if unsatisfactory response), 10 mg/kg/day (if during the previous period will receive this dose)

**Tapering-off \follow-up period:**

After the 12-week maintenance period, the study treatment will be tapered off in 10 mg/kg/day steps every 2 weeks, followed by a 4 week observational follow-up period.

| <b>Number of subjects in period<br/>1[2]</b> | Part I - Placebo | Part I - ESL |
|--|------------------|--------------|
| Started                                      | 129              | 134          |
| Completed                                    | 118              | 120          |
| Not completed                                | 11               | 14           |
| Adverse event, serious fatal                 | 1                | 1            |
| Consent withdrawn by subject                 | 5                | 5            |
| Physician decision                           | 2                | 2            |
| Adverse event, non-fatal                     | 1                | 2            |
| Other reason                                 | 1                | -            |
| Adverse event, serious non-fatal             | -                | 2            |

|  |   |   |
|--|---|---|
| Not serious AE and lack of efficacy            | - | 1 |
| Treatment with > 2 conc. AEDs at the same time | - | 1 |
| Lack of efficacy                               | 1 | - |

Notes:

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

Justification: Baseline period does not include 41 subjects with IMP recall.

**Period 2**

|                              |                                      |
|------------------------------|--------------------------------------|
| Period 2 title               | PART II: OPEN-LABEL EXTENSION PERIOD |
| Is this the baseline period? | No                                   |
| Allocation method            | Not applicable                       |
| Blinding used                | Not blinded                          |

**Arms**

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | Part II - ESL |
|------------------|---------------|

Arm description:

Patients aged 2–6 years will receive the study treatment as 50 mg/mL Eslicarbazepine Acetate oral suspension. Patients aged 7 or over will receive the study treatment in the form of 200 mg Eslicarbazepine Acetate tablets. The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily. Subjects without IMP recall.

|  |                         |
|--|-------------------------|
| Arm type                               | Active comparator       |
| Investigational medicinal product name | Eslicarbazepine acetate |
| Investigational medicinal product code | BIA 2093                |
| Other name                             | Zebinix                 |
| Pharmaceutical forms                   | Tablet, Oral suspension |
| Routes of administration               | Oral use                |

Dosage and administration details:

The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily.

The starting dose will be 10 mg/kg/day or 800 mg/day for patients with high body weight. The daily dose will be titrated by the investigator according to clinical response in the dose range from 10 mg/kg/day to 30 mg/kg/day (or 800 mg/day to maximum 1200 mg/day for patients with high body weight). Down-titration will be allowed during Part II according to clinical response or in case of intolerable AEs.

|   |               |
|---|---------------|
| <b>Number of subjects in period 2<sup>[3]</sup></b> | Part II - ESL |
| Started   | 226           |
| Completed   | 163           |
| Not completed                                       | 63            |
| Consent withdrawn by subject                        | 16            |
| Physician decision                                  | 3             |
| Adverse event, non-fatal                            | 6             |
| At the specific request of the sponsor              | 2             |

|                                  |    |
|----------------------------------|----|
| Other reason                     | 3  |
| Adverse event, serious non-fatal | 3  |
| Lack of efficacy                 | 30 |

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Number of subjects 238 completed double blind part and 12 of them did not start open label part.

**Period 3**

|                              |   |
|------------------------------|---|
| Period 3 title               | PART III-V: OPEN-LABEL EXTENSION PERIOD |
| Is this the baseline period? | No                                      |
| Allocation method            | Not applicable                          |
| Blinding used                | Not blinded                             |

**Arms**

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Part III - V - ESL |
|------------------|--------------------|

Arm description:

Patients aged 2–6 years will receive the study treatment as 50 mg/mL Eslicarbazepine Acetate oral suspension. Patients aged 7 or over will receive the study treatment in the form of 200 mg Eslicarbazepine Acetate tablets. The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily. Subjects without IMP recall.

|  |                         |
|--|-------------------------|
| Arm type                               | Active comparator       |
| Investigational medicinal product name | Eslicarbazepine acetate |
| Investigational medicinal product code | BIA 2093                |
| Other name                             | Zebinix                 |
| Pharmaceutical forms                   | Tablet, Oral suspension |
| Routes of administration               | Oral use                |

Dosage and administration details:

Part III starting dose will be the same dose of Eslicarbazepine Acetate that patient was receiving at the end of the Part II, unless investigator decides to titrate this dose to achieve further reduction in seizure frequency or due to the occurrence of any intolerable AEs. Eslicarbazepine Acetate dose titration schema during this study extension (Part III) will be the same defined for study Part II. The daily dose will be titrated by the investigator according to clinical response in the dose range from 10 mg/kg/day to 30 mg/kg/day (or 800 mg/day to maximum 1200 mg/day for patients with high body weight). The maximum Eslicarbazepine Acetate dosage will be 1200 mg once daily. Down-titration will be allowed during Part III according to clinical response or in case of intolerable AEs.

The same dosage will be applied in the Part IV and Part V as in the Part III.

|   |                    |
|---|--------------------|
| <b>Number of subjects in period 3<sup>[4]</sup></b> | Part III - V - ESL |
| Started   | 152                |
| Completed   | 4                  |
| Not completed                                       | 148                |
| Adverse event, serious fatal                        | 1                  |
| Consent withdrawn by subject                        | 12                 |
| Physician decision                                  | 1                  |

|  |    |
|--|----|
| Switched to Zebinix                    | 3  |
| Discontinued after Part III            | 26 |
| At the specific request of the sponsor | 82 |
| Other reason                           | 4  |
| Lost to follow-up                      | 3  |
| Discontinued after Part IV             | 6  |
| Lack of efficacy                       | 10 |

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Notes:

[4] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Number of subjects 163 completed Part II and 11 of them did not start Part III-V.

## Baseline characteristics

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Part I - Placebo |
|-----------------------|------------------|

Reporting group description:

Patients aged 2–6 years will receive the study treatment as 50 mg/mL placebo oral suspension. Patients aged 7 or over will receive the study treatment in the form of 200 mg placebo tablets. The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily. Subjects without IMP recall.

|                       |              |
|-----------------------|--------------|
| Reporting group title | Part I - ESL |
|-----------------------|--------------|

Reporting group description:

Patients aged 2–6 years will receive the study treatment as 50 mg/mL Eslicarbazepine Acetate oral suspension. Patients aged 7 or over will receive the study treatment in the form of 200 mg Eslicarbazepine Acetate tablets. The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily. Subjects without IMP recall.

| Reporting group values                   | Part I - Placebo | Part I - ESL | Total |
|--|------------------|--------------|-------|
| Number of subjects                       | 129              | 134          | 263   |
| Age Categorical                          |                  |              |       |
| Age Categorical Characteristic           |                  |              |       |
| Units: Subjects                          |                  |              |       |
| In Utero                                 | 0                | 0            | 0     |
| Preterm newborn- gestational age < 37 wk | 0                | 0            | 0     |
| Newborns (0-27days)                      | 0                | 0            | 0     |
| Infants and toddlers (28days - 23months) | 0                | 0            | 0     |
| Children (2-11 years)                    | 84               | 82           | 166   |
| Adolescents (12-17 year)                 | 45               | 51           | 96    |
| From 18 - 64 years                       | 0                | 1            | 1     |
| From 65 - 84 years                       | 0                | 0            | 0     |
| Over 85 years                            | 0                | 0            | 0     |
| Age Continuous                           |                  |              |       |
| Age Continuous Characteristic            |                  |              |       |
| Units: Years                             |                  |              |       |
| arithmetic mean                          | 9.5              | 9.9          |       |
| standard deviation                       | ± 3.85           | ± 4.22       | -     |
| Gender Categorical                       |                  |              |       |
| Gender Categorical Characteristic        |                  |              |       |
| Units: Subjects                          |                  |              |       |
| Female                                   | 67               | 70           | 137   |
| Male                                     | 62               | 64           | 126   |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | Part I - Placebo                       |
| Reporting group description:<br>Patients aged 2–6 years will receive the study treatment as 50 mg/mL placebo oral suspension. Patients aged 7 or over will receive the study treatment in the form of 200 mg placebo tablets. The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily. Subjects without IMP recall.                                 |  |
| Reporting group title   | Part I - ESL                           |
| Reporting group description:<br>Patients aged 2–6 years will receive the study treatment as 50 mg/mL Eslicarbazepine Acetate oral suspension. Patients aged 7 or over will receive the study treatment in the form of 200 mg Eslicarbazepine Acetate tablets. The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily. Subjects without IMP recall. |  |
| Reporting group title   | Part II - ESL                          |
| Reporting group description:<br>Patients aged 2–6 years will receive the study treatment as 50 mg/mL Eslicarbazepine Acetate oral suspension. Patients aged 7 or over will receive the study treatment in the form of 200 mg Eslicarbazepine Acetate tablets. The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily. Subjects without IMP recall. |  |
| Reporting group title   | Part III - V - ESL                     |
| Reporting group description:<br>Patients aged 2–6 years will receive the study treatment as 50 mg/mL Eslicarbazepine Acetate oral suspension. Patients aged 7 or over will receive the study treatment in the form of 200 mg Eslicarbazepine Acetate tablets. The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily. Subjects without IMP recall. |  |
| Subject analysis set title  | Part I - Placebo x Safety Set          |
| Subject analysis set type   | Safety analysis                        |
| Subject analysis set description:<br>All patients who received at least one dose of double-blind study treatment excluding those stratum I patients who were randomised before the IMP recall   |  |
| Subject analysis set title  | Part I - ESL x Safety Set              |
| Subject analysis set type   | Safety analysis                        |
| Subject analysis set description:<br>All patients who received at least one dose of double-blind study treatment excluding those stratum I patients who were randomised before the IMP recall   |  |
| Subject analysis set title  | Part I - Placebo x Intent-to-treat Set |
| Subject analysis set type   | Intention-to-treat                     |
| Subject analysis set description:<br>All patients randomised, treated with at least one dose of study medication after randomisation, and with at least one post-baseline seizure frequency assessment excluding those stratum I patients who were randomised before the IMP recall   |  |
| Subject analysis set title  | Part I - ESL x Intent-to-treat Set     |
| Subject analysis set type   | Intention-to-treat                     |
| Subject analysis set description:<br>All patients randomised, treated with at least one dose of study medication after randomisation, and with at least one post-baseline seizure frequency assessment excluding those stratum I patients who were randomised before the IMP recall   |  |
| Subject analysis set title  | Part I - Placebo x Per Protocol Set    |
| Subject analysis set type   | Per protocol                           |
| Subject analysis set description:<br>All patients of the ITT without any major protocol deviations  |  |
| Subject analysis set title  | Part I - ESL x Per Protocol Set        |

|  |  |
|--|--|
| Subject analysis set type  | Per protocol                           |
| Subject analysis set description:<br>All patients of the ITT without any major protocol deviations   |  |
| Subject analysis set title   | Part II - ESL x Safety Set             |
| Subject analysis set type  | Safety analysis                        |
| Subject analysis set description:<br>All patients entering Part II who received at least one dose of Eslicarbazepine Acetate during the open-label extension period excluding stratum I patients randomised before the IMP recall irrespective of treatment with suspension or tablets in Part II  |  |
| Subject analysis set title   | Part II - ESL x Intent-to-treat Set    |
| Subject analysis set type  | Intention-to-treat                     |
| Subject analysis set description:<br>All patients entering Part II, treated with at least one dose of Eslicarbazepine Acetate during the open-label extension period, and with at least one seizure frequency assessment during the extension period excluding stratum I patients randomised before the IMP recall irrespective of treatment with suspension or tablets in Part II |  |
| Subject analysis set title   | Part III-V - ESL x Safety Set          |
| Subject analysis set type  | Safety analysis                        |
| Subject analysis set description:<br>All patients entering Part III – V, treated with at least one dose of Eslicarbazepine Acetate during the open-label extension period (Part III – V)   |  |
| Subject analysis set title   | Part III-V - ESL x Intent-to-treat Set |
| Subject analysis set type  | Intention-to-treat                     |
| Subject analysis set description:<br>All patients entering Part III – V, treated with at least one dose of Eslicarbazepine Acetate during the open-label extension period (Part III – V), and with at least one seizure frequency assessment during the extension period (Part III – V)  |  |

### Primary: Responder rate in the Part I

|   |                              |
|---|------------------------------|
| End point title   | Responder rate in the Part I |
| End point description:<br>Responder rate defined as the number of patients with at least a 50% decrease in the standardised 4-week seizure frequency from the baseline period to the 12-week maintenance period |                              |
| End point type  | Primary                      |
| End point timeframe:<br>Baseline up to Visit 7 in the Part I  |                              |

| End point values            | Part I - Placebo x Intent-to-treat Set | Part I - ESL x Intent-to-treat Set |  |  |
|-----------------------------|--|------------------------------------|--|--|
| Subject group type          | Subject analysis set                   | Subject analysis set               |  |  |
| Number of subjects analysed | 129                                    | 134                                |  |  |
| Units: Participants         |  |                                    |  |  |
| number (not applicable)     |  |                                    |  |  |
| Participants                | 40                                     | 41                                 |  |  |

### Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Cochran—Mantel—Haenszel—test strat. by age stratum                          |
| Statistical analysis description:<br>The responder rate during the 12-week maintenance period were analysed by a Cochran-Mantel-Haenszel (CMH) test with age stratum as stratification factor. |   |
| Comparison groups  | Part I - Placebo x Intent-to-treat Set v Part I - ESL x Intent-to-treat Set |
| Number of subjects included in analysis  | 263   |
| Analysis specification   | Pre-specified   |
| Analysis type  | equivalence   |
| P-value  | = 0.9017  |
| Method   | Cochran-Mantel-Haenszel   |
| Parameter estimate   | Odds ratio (OR)   |
| Point estimate   | 0.97  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | 0.57  |
| upper limit  | 1.63  |

### Primary: Relative Reduction From Baseline in Seizure Frequency in the Part I

|  |   |
|--|---|
| End point title  | Relative Reduction From Baseline in Seizure Frequency in the Part I |
| End point description:<br>Relative reduction in the standardised 4-week seizure frequency from the baseline period to the 12-week maintenance period |   |
| End point type   | Primary   |
| End point timeframe:<br>Baseline up to Visit 7 in the Part I   |   |

| End point values                    | Part I - Placebo x Intent-to-treat Set | Part I - ESL x Intent-to-treat Set |  |  |
|-------------------------------------|--|------------------------------------|--|--|
| Subject group type                  | Subject analysis set                   | Subject analysis set               |  |  |
| Number of subjects analysed         | 129                                    | 134                                |  |  |
| Units: Seizures                     |  |                                    |  |  |
| least squares mean (standard error) |  |                                    |  |  |
| Seizures                            | -8.6 (± 5.93)                          | -18.1 (± 5.84)                     |  |  |

### Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | ANCOVA model for comparison   |
| Statistical analysis description:<br>ANCOVA model with treatment and stratum group as fixed effects and baseline seizure frequency as a covariate. |   |
| Comparison groups  | Part I - Placebo x Intent-to-treat Set v Part I - ESL x Intent-to-treat Set |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 263                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | equivalence                |
| P-value                                 | = 0.249                    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LS mean                    |
| Point estimate                          | 9.5                        |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -6.71                      |
| upper limit                             | 25.77                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 8.25                       |

### Primary: Relative Change From Baseline in Seizure Frequency in the Part I

|                 |   |
|-----------------|---|
| End point title | Relative Change From Baseline in Seizure Frequency in the Part I <sup>[1]</sup> |
|-----------------|---|

End point description:

Relative change in the standardised 4-week seizure frequency from the baseline period to the 12-week maintenance period

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

End point timeframe:

Baseline up to Visit 7 in the Part I

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 analysis was performed for this end point.

| End point values                     | Part I - Placebo x Intent-to-treat Set | Part I - ESL x Intent-to-treat Set |  |  |
|--------------------------------------|--|------------------------------------|--|--|
| Subject group type                   | Subject analysis set                   | Subject analysis set               |  |  |
| Number of subjects analysed          | 129                                    | 134                                |  |  |
| Units: Seizures                      |  |                                    |  |  |
| arithmetic mean (standard deviation) |  |                                    |  |  |
| Seizures                             | -9.6 (± 70.15)                         | -19.2 (± 64.1)                     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Responder rate in the Part II

|                 |  |
|-----------------|--|
| End point title | Responder rate in the Part II <sup>[2]</sup> |
|-----------------|--|

End point description:

Responder rate defined as the number of patients with at least a 50% decrease in the standardised 4-week seizure frequency

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

End point timeframe:

Baseline till the end of Part II

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 analysis was performed for this end point.

|                             |                                     |  |  |  |
|-----------------------------|-------------------------------------|--|--|--|
| <b>End point values</b>     | Part II - ESL x Intent-to-treat Set |  |  |  |
| Subject group type          | Subject analysis set                |  |  |  |
| Number of subjects analysed | 225                                 |  |  |  |
| Units: Participants         |                                     |  |  |  |
| number (not applicable)     |                                     |  |  |  |
| Participants                | 105                                 |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Relative Change From Baseline in Seizure Frequency in the Part II

End point title | Relative Change From Baseline in Seizure Frequency in the Part II<sup>[3]</sup>

End point description:

Relative change in the standardised 4-week seizure frequency

End point type | Primary

End point timeframe:

Baseline till the end of Part II

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 analysis was performed for this end point.

|                                      |                                     |  |  |  |
|--------------------------------------|-------------------------------------|--|--|--|
| <b>End point values</b>              | Part II - ESL x Intent-to-treat Set |  |  |  |
| Subject group type                   | Subject analysis set                |  |  |  |
| Number of subjects analysed          | 225                                 |  |  |  |
| Units: Seizures                      |                                     |  |  |  |
| arithmetic mean (standard deviation) |                                     |  |  |  |
| Seizures                             | -33.9 (± 58.65)                     |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Responder rate in the Part III-V

End point title | Responder rate in the Part III-V<sup>[4]</sup>

End point description:

Responder rate defined as the number of patients with at least a 50% decrease in the standardised 4-week seizure frequency

End point type Primary

End point timeframe:

Baseline till the end of Part III-V

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 analysis was performed for this end point.

| End point values            | Part III-V - ESL<br>x Intent-to-<br>treat Set |  |  |  |
|-----------------------------|---|--|--|--|
| Subject group type          | Subject analysis set                          |  |  |  |
| Number of subjects analysed | 148   |  |  |  |
| Units: Participants         |   |  |  |  |
| number (not applicable)     |   |  |  |  |
| Participants                | 104   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Relative Change From Baseline in Seizure Frequency in the Part III

End point title Relative Change From Baseline in Seizure Frequency in the Part III<sup>[5]</sup>

End point description:

Relative change in the standardised 4-week seizure frequency

End point type Primary

End point timeframe:

Baseline till the end of Part III

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 analysis was performed for this end point.

| End point values                     | Part III-V - ESL<br>x Intent-to-<br>treat Set |  |  |  |
|--------------------------------------|---|--|--|--|
| Subject group type                   | Subject analysis set                          |  |  |  |
| Number of subjects analysed          | 148   |  |  |  |
| Units: Seizures                      |   |  |  |  |
| arithmetic mean (standard deviation) |   |  |  |  |
| Seizures                             | -58.9 (±<br>50.58)                            |  |  |  |

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the date of first study treatment up to 28 days after the last dose of study medication in the corresponding part.

Adverse event reporting additional description:

Part I: up to the date of visit FU1 for patients continuing if the visit occurs within these 28 days

Part II: up to 28 days after the last dose of IMP for patients discontinuing treatment during Part II or the date of Visit OL6 for patients continuing with treatment in Part III of the study

Part III-V: up to 28 days after the last dose of IMP

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 15.0 |
|--------------------|------|

### Reporting groups

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Part I - Placebo x Safety Set |
|-----------------------|-------------------------------|

Reporting group description:

Subjects in the Safety Set treated with placebo during Part I

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Part I - ESL x Safety Set |
|-----------------------|---------------------------|

Reporting group description:

Subjects in the Safety Set treated with ESL during Part I

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Part II - ESL x Safety Set |
|-----------------------|----------------------------|

Reporting group description:

Subjects in the Safety Set treated with ESL during Part II

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Part III-V - ESL x Safety Set |
|-----------------------|-------------------------------|

Reporting group description:

Subjects in the Safety Set treated with ESL during Part III - V

| <b>Serious adverse events</b>                     | Part I - Placebo x Safety Set | Part I - ESL x Safety Set | Part II - ESL x Safety Set |
|---|-------------------------------|---------------------------|----------------------------|
| Total subjects affected by serious adverse events |                               |                           |                            |
| subjects affected / exposed                       | 9 / 129 (6.98%)               | 15 / 134 (11.19%)         | 23 / 226 (10.18%)          |
| number of deaths (all causes)                     | 1                             | 1                         | 0                          |
| number of deaths resulting from adverse events    | 0                             | 0                         | 0                          |
| Vascular disorders                                |                               |                           |                            |
| Haematoma   |                               |                           |                            |
| subjects affected / exposed                       | 0 / 129 (0.00%)               | 0 / 134 (0.00%)           | 1 / 226 (0.44%)            |
| occurrences causally related to treatment / all   | 0 / 0                         | 0 / 0                     | 0 / 1                      |
| deaths causally related to treatment / all        | 0 / 0                         | 0 / 0                     | 0 / 0                      |
| Surgical and medical procedures                   |                               |                           |                            |
| Medical device change                             |                               |                           |                            |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                                 | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>General disorders and administration site conditions</b> |                 |                 |                 |
| Device malfunction  |                 |                 |                 |
| subjects affected / exposed                                 | 0 / 129 (0.00%) | 2 / 134 (1.49%) | 0 / 226 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 0           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| Drug withdrawal syndrome                                    |                 |                 |                 |
| subjects affected / exposed                                 | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (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           |
| Irritability  |                 |                 |                 |
| subjects affected / exposed                                 | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences causally related to treatment / all             | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Respiratory, thoracic and mediastinal disorders</b>      |                 |                 |                 |
| Asphyxia  |                 |                 |                 |
| subjects affected / exposed                                 | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                  | 0 / 1           | 0 / 0           | 0 / 0           |
| Asthma  |                 |                 |                 |
| subjects affected / exposed                                 | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (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           |
| Epistaxis   |                 |                 |                 |
| subjects affected / exposed                                 | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (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>Psychiatric disorders</b>                                |                 |                 |                 |
| Conduct disorder  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                           | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Investigations</b>                                 |                 |                 |                 |
| <b>Aspartate aminotransferase increased</b>           |                 |                 |                 |
| subjects affected / exposed                           | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Gamma-glutamyltransferase increased</b>            |                 |                 |                 |
| subjects affected / exposed                           | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 2 / 226 (0.88%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           | 2 / 2           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Hepatic enzyme increased</b>                       |                 |                 |                 |
| subjects affected / exposed                           | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (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>Injury, poisoning and procedural complications</b> |                 |                 |                 |
| <b>Brain herniation</b>                               |                 |                 |                 |
| subjects affected / exposed                           | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (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           |
| <b>Concussion</b>                                     |                 |                 |                 |
| subjects affected / exposed                           | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (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>Head injury</b>                                    |                 |                 |                 |
| subjects affected / exposed                           | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (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>Joint dislocation</b>                              |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Nervous system disorders</b>                 |                 |                 |                 |
| <b>Ataxia</b>                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Brain oedema</b>                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (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           |
| <b>Convulsion</b>                               |                 |                 |                 |
| subjects affected / exposed                     | 2 / 129 (1.55%) | 2 / 134 (1.49%) | 6 / 226 (2.65%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 2           | 1 / 7           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| <b>Dysarthria</b>                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Epilepsy</b>                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 1 / 226 (0.44%) |
| 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>Febrile convulsion</b>                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (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>Grand mal convulsion</b>                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Hydrocephalus</b>                            |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                           | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Hypotonia</b>                                      |                 |                 |                 |
| subjects affected / exposed                           | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences causally related to treatment / all       | 1 / 1           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Nystagmus</b>                                      |                 |                 |                 |
| subjects affected / exposed                           | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Partial seizures with secondary generalisation</b> |                 |                 |                 |
| subjects affected / exposed                           | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 1 / 226 (0.44%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           | 1 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Status epilepticus</b>                             |                 |                 |                 |
| subjects affected / exposed                           | 0 / 129 (0.00%) | 3 / 134 (2.24%) | 2 / 226 (0.88%) |
| occurrences causally related to treatment / all       | 0 / 0           | 1 / 3           | 0 / 2           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Ear and labyrinth disorders</b>                    |                 |                 |                 |
| <b>Otosalpingitis</b>                                 |                 |                 |                 |
| subjects affected / exposed                           | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Vertigo</b>  |                 |                 |                 |
| subjects affected / exposed                           | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Eye disorders</b>                                  |                 |                 |                 |
| <b>Diplopia</b>                                       |                 |                 |                 |
| subjects affected / exposed                           | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Gastrointestinal disorders                      |                 |                 |                 |
| Abdominal hernia                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (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           |
| Coeliac disease                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (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           |
| Colitis   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ileus   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (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 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vomiting  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |
| Rash vesicular                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urticaria                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Vascular purpura                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (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           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Osteochondrosis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| 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                     |                 |                 |                 |
| Abdominal wall abscess                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (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           |
| Abscess neck                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (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           |
| Bronchopneumonia                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 2 / 134 (1.49%) | 1 / 226 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dengue fever                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (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           |
| Gastroenteritis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infectious mononucleosis                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Lobar pneumonia                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung abscess                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (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           |
| Pharyngitis                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 3 / 129 (2.33%) | 1 / 134 (0.75%) | 4 / 226 (1.77%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory tract infection                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Varicella                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Viral infection                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (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           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Dehydration                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyponatraemia                                   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

| <b>Serious adverse events</b>                        | Part III-V - ESL x Safety Set |  |  |
|--|-------------------------------|--|--|
| Total subjects affected by serious adverse events    |                               |  |  |
| subjects affected / exposed                          | 16 / 152 (10.53%)             |  |  |
| number of deaths (all causes)                        | 1                             |  |  |
| number of deaths resulting from adverse events       | 0                             |  |  |
| Vascular disorders                                   |                               |  |  |
| Haematoma  |                               |  |  |
| subjects affected / exposed                          | 0 / 152 (0.00%)               |  |  |
| occurrences causally related to treatment / all      | 0 / 0                         |  |  |
| deaths causally related to treatment / all           | 0 / 0                         |  |  |
| Surgical and medical procedures                      |                               |  |  |
| Medical device change                                |                               |  |  |
| subjects affected / exposed                          | 0 / 152 (0.00%)               |  |  |
| occurrences causally related to treatment / all      | 0 / 0                         |  |  |
| deaths causally related to treatment / all           | 0 / 0                         |  |  |
| General disorders and administration site conditions |                               |  |  |
| Device malfunction                                   |                               |  |  |
| subjects affected / exposed                          | 1 / 152 (0.66%)               |  |  |
| occurrences causally related to treatment / all      | 0 / 2                         |  |  |
| deaths causally related to treatment / all           | 0 / 0                         |  |  |
| Drug withdrawal syndrome                             |                               |  |  |
| subjects affected / exposed                          | 0 / 152 (0.00%)               |  |  |
| occurrences causally related to treatment / all      | 0 / 0                         |  |  |
| deaths causally related to treatment / all           | 0 / 0                         |  |  |
| Irritability   |                               |  |  |
| subjects affected / exposed                          | 0 / 152 (0.00%)               |  |  |
| occurrences causally related to treatment / all      | 0 / 0                         |  |  |
| deaths causally related to treatment / all           | 0 / 0                         |  |  |
| Respiratory, thoracic and mediastinal disorders      |                               |  |  |
| Asphyxia   |                               |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                           | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all       | 0 / 0           |  |  |
| deaths causally related to treatment / all            | 0 / 0           |  |  |
| <b>Asthma</b>   |                 |  |  |
| subjects affected / exposed                           | 2 / 152 (1.32%) |  |  |
| occurrences causally related to treatment / all       | 0 / 2           |  |  |
| deaths causally related to treatment / all            | 0 / 0           |  |  |
| <b>Epistaxis</b>                                      |                 |  |  |
| subjects affected / exposed                           | 1 / 152 (0.66%) |  |  |
| occurrences causally related to treatment / all       | 0 / 1           |  |  |
| deaths causally related to treatment / all            | 0 / 0           |  |  |
| <b>Psychiatric disorders</b>                          |                 |  |  |
| <b>Conduct disorder</b>                               |                 |  |  |
| subjects affected / exposed                           | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all       | 0 / 0           |  |  |
| deaths causally related to treatment / all            | 0 / 0           |  |  |
| <b>Investigations</b>                                 |                 |  |  |
| <b>Aspartate aminotransferase increased</b>           |                 |  |  |
| subjects affected / exposed                           | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all       | 0 / 0           |  |  |
| deaths causally related to treatment / all            | 0 / 0           |  |  |
| <b>Gamma-glutamyltransferase increased</b>            |                 |  |  |
| subjects affected / exposed                           | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all       | 0 / 0           |  |  |
| deaths causally related to treatment / all            | 0 / 0           |  |  |
| <b>Hepatic enzyme increased</b>                       |                 |  |  |
| subjects affected / exposed                           | 1 / 152 (0.66%) |  |  |
| occurrences causally related to treatment / all       | 0 / 1           |  |  |
| deaths causally related to treatment / all            | 0 / 0           |  |  |
| <b>Injury, poisoning and procedural complications</b> |                 |  |  |
| <b>Brain herniation</b>                               |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Concussion</b>                               |                 |  |  |
| subjects affected / exposed                     | 1 / 152 (0.66%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Head injury</b>                              |                 |  |  |
| subjects affected / exposed                     | 1 / 152 (0.66%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Joint dislocation</b>                        |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Nervous system disorders</b>                 |                 |  |  |
| <b>Ataxia</b>                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Brain oedema</b>                             |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Convulsion</b>                               |                 |  |  |
| subjects affected / exposed                     | 2 / 152 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Dysarthria</b>                               |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Epilepsy</b>                                 |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Febrile convulsion                              |                 |  |  |
| subjects affected / exposed                     | 1 / 152 (0.66%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Grand mal convulsion                            |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hydrocephalus                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypotonia                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nystagmus                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Partial seizures with secondary generalisation  |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Status epilepticus                              |                 |  |  |
| subjects affected / exposed                     | 2 / 152 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ear and labyrinth disorders                     |                 |  |  |
| Otosalpingitis                                  |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vertigo   |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Eye disorders                                   |                 |  |  |
| Diplopia  |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Abdominal hernia                                |                 |  |  |
| subjects affected / exposed                     | 1 / 152 (0.66%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Coeliac disease                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Colitis   |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ileus   |                 |  |  |
| subjects affected / exposed                     | 1 / 152 (0.66%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pancreatitis acute                              |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vomiting  |                 |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                            | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all        | 0 / 0           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Skin and subcutaneous tissue disorders</b>          |                 |  |  |
| Rash vesicular   |                 |  |  |
| subjects affected / exposed                            | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all        | 0 / 0           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| Urticaria  |                 |  |  |
| subjects affected / exposed                            | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all        | 0 / 0           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| Vascular purpura                                       |                 |  |  |
| subjects affected / exposed                            | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all        | 0 / 0           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Musculoskeletal and connective tissue disorders</b> |                 |  |  |
| Osteochondrosis  |                 |  |  |
| subjects affected / exposed                            | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all        | 0 / 0           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Infections and infestations</b>                     |                 |  |  |
| Abdominal wall abscess                                 |                 |  |  |
| subjects affected / exposed                            | 1 / 152 (0.66%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| Abscess neck   |                 |  |  |
| subjects affected / exposed                            | 1 / 152 (0.66%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| Bronchopneumonia                                       |                 |  |  |
| subjects affected / exposed                            | 2 / 152 (1.32%) |  |  |
| occurrences causally related to treatment / all        | 0 / 2           |  |  |
| deaths causally related to treatment / all             | 0 / 1           |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| Dengue fever                                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 152 (0.66%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gastroenteritis                                 |                 |  |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Infectious mononucleosis                        |                 |  |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Lobar pneumonia                                 |                 |  |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Lung abscess                                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 152 (0.66%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pharyngitis                                     |                 |  |  |  |
| subjects affected / exposed                     | 1 / 152 (0.66%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumonia                                       |                 |  |  |  |
| subjects affected / exposed                     | 2 / 152 (1.32%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Respiratory tract infection                     |                 |  |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Varicella                                       |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Viral infection                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Dehydration                                     |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hyponatraemia                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

| <b>Non-serious adverse events</b>                                   | Part I - Placebo x Safety Set | Part I - ESL x Safety Set | Part II - ESL x Safety Set |
|---|-------------------------------|---------------------------|----------------------------|
| Total subjects affected by non-serious adverse events               |                               |                           |                            |
| subjects affected / exposed   | 92 / 129 (71.32%)             | 108 / 134 (80.60%)        | 172 / 226 (76.11%)         |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                               |                           |                            |
| Oral papilloma  |                               |                           |                            |
| subjects affected / exposed   | 0 / 129 (0.00%)               | 1 / 134 (0.75%)           | 0 / 226 (0.00%)            |
| occurrences (all)   | 0                             | 1                         | 0                          |
| Sebaceous adenoma   |                               |                           |                            |
| subjects affected / exposed   | 0 / 129 (0.00%)               | 1 / 134 (0.75%)           | 0 / 226 (0.00%)            |
| occurrences (all)   | 0                             | 1                         | 0                          |
| Skin papilloma  |                               |                           |                            |
| subjects affected / exposed   | 0 / 129 (0.00%)               | 1 / 134 (0.75%)           | 1 / 226 (0.44%)            |
| occurrences (all)   | 0                             | 1                         | 1                          |
| Vascular disorders  |                               |                           |                            |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| Haematoma  |                 |                 |                 |
| subjects affected / exposed                          | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)                                    | 2               | 0               | 0               |
| Hypertension   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)                                    | 0               | 0               | 1               |
| Phlebitis  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)                                    | 0               | 1               | 0               |
| Systolic hypertension                                |                 |                 |                 |
| subjects affected / exposed                          | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)                                    | 0               | 0               | 0               |
| Surgical and medical procedures                      |                 |                 |                 |
| Adenoidectomy  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)                                    | 0               | 1               | 0               |
| Brain operation                                      |                 |                 |                 |
| subjects affected / exposed                          | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)                                    | 0               | 1               | 0               |
| Plastic surgery to the face                          |                 |                 |                 |
| subjects affected / exposed                          | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)                                    | 0               | 0               | 1               |
| Suture insertion                                     |                 |                 |                 |
| subjects affected / exposed                          | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)                                    | 0               | 0               | 1               |
| Tenotomy   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)                                    | 0               | 0               | 1               |
| Tooth extraction                                     |                 |                 |                 |
| subjects affected / exposed                          | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)                                    | 1               | 0               | 1               |
| General disorders and administration site conditions |                 |                 |                 |
| Asthenia   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 129 (0.00%) | 2 / 134 (1.49%) | 3 / 226 (1.33%) |
| occurrences (all)                                    | 0               | 2               | 3               |
| Chest pain   |                 |                 |                 |

|                             |                 |                  |                  |
|-----------------------------|-----------------|------------------|------------------|
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%)  | 1 / 226 (0.44%)  |
| occurrences (all)           | 0               | 0                | 1                |
| Device malfunction          |                 |                  |                  |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 134 (0.00%)  | 0 / 226 (0.00%)  |
| occurrences (all)           | 1               | 0                | 0                |
| Face oedema                 |                 |                  |                  |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%)  | 1 / 226 (0.44%)  |
| occurrences (all)           | 0               | 0                | 1                |
| Fatigue                     |                 |                  |                  |
| subjects affected / exposed | 3 / 129 (2.33%) | 5 / 134 (3.73%)  | 6 / 226 (2.65%)  |
| occurrences (all)           | 3               | 7                | 6                |
| Feeling hot                 |                 |                  |                  |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 134 (0.75%)  | 0 / 226 (0.00%)  |
| occurrences (all)           | 0               | 1                | 0                |
| Gait disturbance            |                 |                  |                  |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 134 (0.75%)  | 4 / 226 (1.77%)  |
| occurrences (all)           | 0               | 2                | 4                |
| Hyperthermia                |                 |                  |                  |
| subjects affected / exposed | 1 / 129 (0.78%) | 2 / 134 (1.49%)  | 2 / 226 (0.88%)  |
| occurrences (all)           | 1               | 2                | 2                |
| Irritability                |                 |                  |                  |
| subjects affected / exposed | 1 / 129 (0.78%) | 2 / 134 (1.49%)  | 4 / 226 (1.77%)  |
| occurrences (all)           | 1               | 2                | 4                |
| Malaise                     |                 |                  |                  |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 134 (0.75%)  | 1 / 226 (0.44%)  |
| occurrences (all)           | 0               | 2                | 2                |
| Oedema                      |                 |                  |                  |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 134 (0.75%)  | 0 / 226 (0.00%)  |
| occurrences (all)           | 0               | 1                | 0                |
| Pain                        |                 |                  |                  |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 134 (0.00%)  | 0 / 226 (0.00%)  |
| occurrences (all)           | 1               | 0                | 0                |
| Pyrexia                     |                 |                  |                  |
| subjects affected / exposed | 7 / 129 (5.43%) | 10 / 134 (7.46%) | 20 / 226 (8.85%) |
| occurrences (all)           | 13              | 14               | 27               |
| Sluggishness                |                 |                  |                  |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                              | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Thirst<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1 | 0 / 226 (0.00%)<br>0 |
| Immune system disorders   |                      |                      |                      |
| Allergy to arthropod bite<br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1 | 0 / 226 (0.00%)<br>0 |
| Drug hypersensitivity<br>subjects affected / exposed<br>occurrences (all)     | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Hypersensitivity<br>subjects affected / exposed<br>occurrences (all)          | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1 | 3 / 226 (1.33%)<br>3 |
| Immunodeficiency<br>subjects affected / exposed<br>occurrences (all)          | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)          | 0 / 129 (0.00%)<br>0 | 2 / 134 (1.49%)<br>2 | 1 / 226 (0.44%)<br>2 |
| Reproductive system and breast disorders                                      |                      |                      |                      |
| Dysmenorrhoea<br>subjects affected / exposed<br>occurrences (all)             | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Epididymal cyst<br>subjects affected / exposed<br>occurrences (all)           | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Labia enlarged<br>subjects affected / exposed<br>occurrences (all)            | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1 | 0 / 226 (0.00%)<br>0 |
| Menstruation irregular<br>subjects affected / exposed<br>occurrences (all)    | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1 | 0 / 226 (0.00%)<br>0 |
| Pelvic pain   |                      |                      |                      |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                           | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Polycystic ovaries<br>subjects affected / exposed<br>occurrences (all)     | 1 / 129 (0.78%)<br>1 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Vaginal discharge<br>subjects affected / exposed<br>occurrences (all)      | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Respiratory, thoracic and mediastinal disorders                            |                      |                      |                      |
| Asthma<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 129 (0.00%)<br>0 | 3 / 134 (2.24%)<br>6 | 1 / 226 (0.44%)<br>3 |
| Bronchospasm<br>subjects affected / exposed<br>occurrences (all)           | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Cough<br>subjects affected / exposed<br>occurrences (all)                  | 4 / 129 (3.10%)<br>4 | 2 / 134 (1.49%)<br>3 | 6 / 226 (2.65%)<br>8 |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)              | 1 / 129 (0.78%)<br>1 | 1 / 134 (0.75%)<br>1 | 3 / 226 (1.33%)<br>3 |
| Laryngospasm<br>subjects affected / exposed<br>occurrences (all)           | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>3 | 1 / 226 (0.44%)<br>3 |
| Nasal discomfort<br>subjects affected / exposed<br>occurrences (all)       | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1 | 0 / 226 (0.00%)<br>0 |
| Nasal obstruction<br>subjects affected / exposed<br>occurrences (all)      | 1 / 129 (0.78%)<br>1 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Nasal septum deviation<br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Oropharyngeal pain   |                      |                      |                      |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                           | 1 / 129 (0.78%)<br>1 | 3 / 134 (2.24%)<br>3 | 4 / 226 (1.77%)<br>5 |
| Respiratory disorder<br>subjects affected / exposed<br>occurrences (all)   | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>3 | 2 / 226 (0.88%)<br>2 |
| Rhinitis allergic<br>subjects affected / exposed<br>occurrences (all)      | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)            | 2 / 129 (1.55%)<br>3 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>3 |
| Tonsillar hypertrophy<br>subjects affected / exposed<br>occurrences (all)  | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Tonsillar inflammation<br>subjects affected / exposed<br>occurrences (all) | 1 / 129 (0.78%)<br>1 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Vasomotor rhinitis<br>subjects affected / exposed<br>occurrences (all)     | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Psychiatric disorders  |                      |                      |                      |
| Abnormal behaviour<br>subjects affected / exposed<br>occurrences (all)     | 1 / 129 (0.78%)<br>1 | 2 / 134 (1.49%)<br>2 | 3 / 226 (1.33%)<br>3 |
| Affect lability<br>subjects affected / exposed<br>occurrences (all)        | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Agitation<br>subjects affected / exposed<br>occurrences (all)              | 1 / 129 (0.78%)<br>1 | 5 / 134 (3.73%)<br>5 | 1 / 226 (0.44%)<br>1 |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1 | 0 / 226 (0.00%)<br>0 |
| Apathy<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 2 / 226 (0.88%)<br>2 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| Attention deficit/Hyperactivity disorder |                 |                 |                 |
| subjects affected / exposed              | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)                        | 1               | 0               | 1               |
| Bradyphrenia                             |                 |                 |                 |
| subjects affected / exposed              | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)                        | 0               | 1               | 0               |
| Bruxism                                  |                 |                 |                 |
| subjects affected / exposed              | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)                        | 0               | 1               | 0               |
| Confusional state                        |                 |                 |                 |
| subjects affected / exposed              | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)                        | 0               | 1               | 0               |
| Depressed mood                           |                 |                 |                 |
| subjects affected / exposed              | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)                        | 1               | 0               | 0               |
| Disorientation                           |                 |                 |                 |
| subjects affected / exposed              | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)                        | 0               | 0               | 1               |
| Dyslogia                                 |                 |                 |                 |
| subjects affected / exposed              | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)                        | 0               | 1               | 0               |
| Dythymic disorder                        |                 |                 |                 |
| subjects affected / exposed              | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)                        | 0               | 1               | 0               |
| Emotional distress                       |                 |                 |                 |
| subjects affected / exposed              | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)                        | 0               | 0               | 0               |
| Encopresis                               |                 |                 |                 |
| subjects affected / exposed              | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)                        | 0               | 0               | 0               |
| Inappropriate affect                     |                 |                 |                 |
| subjects affected / exposed              | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)                        | 0               | 2               | 0               |
| Initial insomnia                         |                 |                 |                 |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                  | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 129 (0.78%)<br>1 | 2 / 134 (1.49%)<br>4 | 1 / 226 (0.44%)<br>1 |
| Listless<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1 | 0 / 226 (0.00%)<br>0 |
| Mood altered<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Mood swings<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 129 (0.00%)<br>0 | 2 / 134 (1.49%)<br>2 | 1 / 226 (0.44%)<br>1 |
| Nervousness<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Obsessive-compulsive disorder<br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Panic attack<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Restlessness<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 129 (0.78%)<br>1 | 1 / 134 (0.75%)<br>2 | 0 / 226 (0.00%)<br>0 |
| Sleep disorder<br>subjects affected / exposed<br>occurrences (all)                | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Sleep talking<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1 | 0 / 226 (0.00%)<br>0 |
| Somatoform disorder<br>subjects affected / exposed<br>occurrences (all)           | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Investigations  |                      |                      |                      |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)          | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)        | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)        | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Blood bicarbonate decreased<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 129 (1.55%)<br>2 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Blood calcium decreased<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 2 / 226 (0.88%)<br>2 |
| Blood creatine phosphokinase increased<br>subjects affected / exposed<br>occurrences (all)      | 2 / 129 (1.55%)<br>2 | 2 / 134 (1.49%)<br>2 | 1 / 226 (0.44%)<br>1 |
| Blood glucose decreased<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Blood lactate dehydrogenase increased<br>subjects affected / exposed<br>occurrences (all)       | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1 | 0 / 226 (0.00%)<br>0 |
| Blood thyroid stimulating hormone increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 129 (0.78%)<br>1 | 2 / 134 (1.49%)<br>2 | 2 / 226 (0.88%)<br>2 |
| Blood triglycerides increased<br>subjects affected / exposed<br>occurrences (all)               | 2 / 129 (1.55%)<br>2 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Body temperature increased<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 129 (0.78%)<br>1 | 1 / 134 (0.75%)<br>1 | 0 / 226 (0.00%)<br>0 |
| Breath sounds abnormal  |                      |                      |                      |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                  | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)                            | 1               | 0               | 0               |
| Ecg p wave inverted                          |                 |                 |                 |
| subjects affected / exposed                  | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)                            | 0               | 0               | 1               |
| Electrocardiogram pr shortened               |                 |                 |                 |
| subjects affected / exposed                  | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)                            | 0               | 0               | 0               |
| Electrocardiogram pr prolongation            |                 |                 |                 |
| subjects affected / exposed                  | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)                            | 0               | 1               | 0               |
| Electrocardiogram qt prolonged               |                 |                 |                 |
| subjects affected / exposed                  | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 1 / 226 (0.44%) |
| occurrences (all)                            | 0               | 1               | 1               |
| Electrocardiogram repolarisation abnormality |                 |                 |                 |
| subjects affected / exposed                  | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)                            | 0               | 0               | 1               |
| Eosinophil count increased                   |                 |                 |                 |
| subjects affected / exposed                  | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)                            | 0               | 0               | 1               |
| Gamma-glutamyltransferase increased          |                 |                 |                 |
| subjects affected / exposed                  | 1 / 129 (0.78%) | 1 / 134 (0.75%) | 7 / 226 (3.10%) |
| occurrences (all)                            | 1               | 1               | 7               |
| Haemoglobin decreased                        |                 |                 |                 |
| subjects affected / exposed                  | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)                            | 0               | 0               | 0               |
| Hepatic enzyme increased                     |                 |                 |                 |
| subjects affected / exposed                  | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)                            | 0               | 0               | 0               |
| Platelet count decreased                     |                 |                 |                 |
| subjects affected / exposed                  | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)                            | 0               | 0               | 0               |
| Platelet count increased                     |                 |                 |                 |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                     | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Positive rombergism<br>subjects affected / exposed<br>occurrences (all)              | 1 / 129 (0.78%)<br>1 | 1 / 134 (0.75%)<br>1 | 3 / 226 (1.33%)<br>4 |
| Rheumatoid factor increased<br>subjects affected / exposed<br>occurrences (all)      | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1 | 0 / 226 (0.00%)<br>0 |
| Thyroxine decreased<br>subjects affected / exposed<br>occurrences (all)              | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Thyroxine increased<br>subjects affected / exposed<br>occurrences (all)              | 1 / 129 (0.78%)<br>1 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Transaminases increased<br>subjects affected / exposed<br>occurrences (all)          | 1 / 129 (0.78%)<br>1 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>2 |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 129 (1.55%)<br>2 | 5 / 134 (3.73%)<br>5 | 3 / 226 (1.33%)<br>3 |
| White blood cell count increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Injury, poisoning and procedural complications                                       |                      |                      |                      |
| Arthropod bite<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 129 (0.78%)<br>1 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Clavicle fracture<br>subjects affected / exposed<br>occurrences (all)                | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Concussion   |                      |                      |                      |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Contusion                   |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 3 / 134 (2.24%) | 0 / 226 (0.00%) |
| occurrences (all)           | 1               | 3               | 0               |
| Drug toxicity               |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)           | 0               | 0               | 1               |
| Excoriation                 |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 1 / 134 (0.75%) | 3 / 226 (1.33%) |
| occurrences (all)           | 2               | 1               | 3               |
| Face injury                 |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)           | 0               | 0               | 3               |
| Fall                        |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 3 / 226 (1.33%) |
| occurrences (all)           | 1               | 0               | 7               |
| Foot fracture               |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)           | 0               | 0               | 1               |
| Forearm fracture            |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Hand fracture               |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)           | 1               | 1               | 0               |
| Head injury                 |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 2 / 134 (1.49%) | 4 / 226 (1.77%) |
| occurrences (all)           | 1               | 2               | 4               |
| Injury                      |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)           | 0               | 0               | 1               |
| Joint injury                |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Laceration                  |                 |                 |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)           | 0               | 0               | 1               |
| Ligament sprain             |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Limb injury                 |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 2 / 134 (1.49%) | 1 / 226 (0.44%) |
| occurrences (all)           | 0               | 2               | 1               |
| Lip injury                  |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Overdose                    |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Poisoning                   |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)           | 0               | 0               | 1               |
| Radius fracture             |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Skin injury                 |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Skin wound                  |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)           | 0               | 0               | 1               |
| Soft tissue injury          |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Thermal burn                |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Tibia fracture              |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Tooth fracture              |                 |                 |                 |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                               | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Tooth injury<br>subjects affected / exposed<br>occurrences (all)               | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Toxicity to various agents<br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Traumatic haematoma<br>subjects affected / exposed<br>occurrences (all)        | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Upper limb fracture<br>subjects affected / exposed<br>occurrences (all)        | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Wound<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1 | 0 / 226 (0.00%)<br>0 |
| Wrist fracture<br>subjects affected / exposed<br>occurrences (all)             | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1 | 1 / 226 (0.44%)<br>1 |
| <b>Congenital, familial and genetic disorders</b>                              |                      |                      |                      |
| Atrial septal defect<br>subjects affected / exposed<br>occurrences (all)       | 1 / 129 (0.78%)<br>1 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Phimosis<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| <b>Cardiac disorders</b>   |                      |                      |                      |
| Arrhythmia<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Bradyarrhythmia<br>subjects affected / exposed<br>occurrences (all)            | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Tachycardia  |                      |                      |                      |

|   |                         |                        |                         |
|---|-------------------------|------------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 129 (0.00%)<br>0    | 1 / 134 (0.75%)<br>2   | 1 / 226 (0.44%)<br>1    |
| Tricuspid valve incompetence<br>subjects affected / exposed<br>occurrences (all)            | 0 / 129 (0.00%)<br>0    | 0 / 134 (0.00%)<br>0   | 0 / 226 (0.00%)<br>0    |
| Wolff-parkinson-white syndrome<br>subjects affected / exposed<br>occurrences (all)          | 0 / 129 (0.00%)<br>0    | 0 / 134 (0.00%)<br>0   | 1 / 226 (0.44%)<br>1    |
| <b>Nervous system disorders</b>   |                         |                        |                         |
| <b>Ataxia</b><br>subjects affected / exposed<br>occurrences (all)                           | 1 / 129 (0.78%)<br>1    | 3 / 134 (2.24%)<br>4   | 2 / 226 (0.88%)<br>2    |
| <b>Balance disorder</b><br>subjects affected / exposed<br>occurrences (all)                 | 0 / 129 (0.00%)<br>0    | 1 / 134 (0.75%)<br>1   | 0 / 226 (0.00%)<br>0    |
| <b>Cerebellar ataxia</b><br>subjects affected / exposed<br>occurrences (all)                | 1 / 129 (0.78%)<br>1    | 3 / 134 (2.24%)<br>3   | 3 / 226 (1.33%)<br>3    |
| <b>Cerebrovascular disorder</b><br>subjects affected / exposed<br>occurrences (all)         | 0 / 129 (0.00%)<br>0    | 1 / 134 (0.75%)<br>1   | 0 / 226 (0.00%)<br>0    |
| <b>Circadian rhythm sleep disorder</b><br>subjects affected / exposed<br>occurrences (all)  | 0 / 129 (0.00%)<br>0    | 0 / 134 (0.00%)<br>0   | 0 / 226 (0.00%)<br>0    |
| <b>Cognitive disorder</b><br>subjects affected / exposed<br>occurrences (all)               | 1 / 129 (0.78%)<br>1    | 0 / 134 (0.00%)<br>0   | 1 / 226 (0.44%)<br>1    |
| <b>Convulsion</b><br>subjects affected / exposed<br>occurrences (all)                       | 13 / 129 (10.08%)<br>18 | 11 / 134 (8.21%)<br>15 | 29 / 226 (12.83%)<br>47 |
| <b>Coordination abnormal</b><br>subjects affected / exposed<br>occurrences (all)            | 0 / 129 (0.00%)<br>0    | 1 / 134 (0.75%)<br>1   | 0 / 226 (0.00%)<br>0    |
| <b>Depressed level of consciousness</b><br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0    | 0 / 134 (0.00%)<br>0   | 0 / 226 (0.00%)<br>0    |

|                             |                 |                   |                  |
|-----------------------------|-----------------|-------------------|------------------|
| Dizziness                   |                 |                   |                  |
| subjects affected / exposed | 2 / 129 (1.55%) | 5 / 134 (3.73%)   | 6 / 226 (2.65%)  |
| occurrences (all)           | 2               | 5                 | 10               |
| Epilepsy                    |                 |                   |                  |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 134 (0.00%)   | 2 / 226 (0.88%)  |
| occurrences (all)           | 1               | 0                 | 2                |
| Head titubation             |                 |                   |                  |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%)   | 1 / 226 (0.44%)  |
| occurrences (all)           | 0               | 0                 | 1                |
| Headache                    |                 |                   |                  |
| subjects affected / exposed | 8 / 129 (6.20%) | 18 / 134 (13.43%) | 20 / 226 (8.85%) |
| occurrences (all)           | 14              | 22                | 26               |
| Hypotonia                   |                 |                   |                  |
| subjects affected / exposed | 1 / 129 (0.78%) | 1 / 134 (0.75%)   | 2 / 226 (0.88%)  |
| occurrences (all)           | 1               | 1                 | 2                |
| Intention tremor            |                 |                   |                  |
| subjects affected / exposed | 1 / 129 (0.78%) | 1 / 134 (0.75%)   | 1 / 226 (0.44%)  |
| occurrences (all)           | 1               | 1                 | 1                |
| Intracranial haematoma      |                 |                   |                  |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%)   | 0 / 226 (0.00%)  |
| occurrences (all)           | 0               | 0                 | 0                |
| Lethargy                    |                 |                   |                  |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 134 (0.75%)   | 1 / 226 (0.44%)  |
| occurrences (all)           | 0               | 1                 | 1                |
| Memory impairment           |                 |                   |                  |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 134 (0.75%)   | 0 / 226 (0.00%)  |
| occurrences (all)           | 0               | 1                 | 0                |
| Mental impairment           |                 |                   |                  |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%)   | 1 / 226 (0.44%)  |
| occurrences (all)           | 0               | 0                 | 1                |
| Migraine                    |                 |                   |                  |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 134 (0.75%)   | 0 / 226 (0.00%)  |
| occurrences (all)           | 0               | 1                 | 0                |
| Nystagmus                   |                 |                   |                  |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 134 (0.75%)   | 3 / 226 (1.33%)  |
| occurrences (all)           | 0               | 1                 | 3                |

|  |                 |                   |                  |
|--|-----------------|-------------------|------------------|
| Paraesthesia                                   |                 |                   |                  |
| subjects affected / exposed                    | 0 / 129 (0.00%) | 0 / 134 (0.00%)   | 1 / 226 (0.44%)  |
| occurrences (all)                              | 0               | 0                 | 1                |
| Partial seizures with secondary generalisation |                 |                   |                  |
| subjects affected / exposed                    | 0 / 129 (0.00%) | 1 / 134 (0.75%)   | 0 / 226 (0.00%)  |
| occurrences (all)                              | 0               | 1                 | 0                |
| Poor quality sleep                             |                 |                   |                  |
| subjects affected / exposed                    | 0 / 129 (0.00%) | 1 / 134 (0.75%)   | 0 / 226 (0.00%)  |
| occurrences (all)                              | 0               | 1                 | 0                |
| Postictal headache                             |                 |                   |                  |
| subjects affected / exposed                    | 1 / 129 (0.78%) | 0 / 134 (0.00%)   | 1 / 226 (0.44%)  |
| occurrences (all)                              | 1               | 0                 | 1                |
| Postictal state                                |                 |                   |                  |
| subjects affected / exposed                    | 0 / 129 (0.00%) | 0 / 134 (0.00%)   | 1 / 226 (0.44%)  |
| occurrences (all)                              | 0               | 0                 | 1                |
| Psychomotor hyperactivity                      |                 |                   |                  |
| subjects affected / exposed                    | 1 / 129 (0.78%) | 1 / 134 (0.75%)   | 1 / 226 (0.44%)  |
| occurrences (all)                              | 1               | 1                 | 1                |
| Somnolence                                     |                 |                   |                  |
| subjects affected / exposed                    | 6 / 129 (4.65%) | 15 / 134 (11.19%) | 20 / 226 (8.85%) |
| occurrences (all)                              | 8               | 16                | 25               |
| Speech disorder                                |                 |                   |                  |
| subjects affected / exposed                    | 0 / 129 (0.00%) | 1 / 134 (0.75%)   | 0 / 226 (0.00%)  |
| occurrences (all)                              | 0               | 1                 | 0                |
| Status epilepticus                             |                 |                   |                  |
| subjects affected / exposed                    | 1 / 129 (0.78%) | 0 / 134 (0.00%)   | 0 / 226 (0.00%)  |
| occurrences (all)                              | 1               | 0                 | 0                |
| Syncope  |                 |                   |                  |
| subjects affected / exposed                    | 1 / 129 (0.78%) | 0 / 134 (0.00%)   | 1 / 226 (0.44%)  |
| occurrences (all)                              | 1               | 0                 | 1                |
| Tremor   |                 |                   |                  |
| subjects affected / exposed                    | 2 / 129 (1.55%) | 2 / 134 (1.49%)   | 3 / 226 (1.33%)  |
| occurrences (all)                              | 2               | 2                 | 3                |
| Unresponsive to stimuli                        |                 |                   |                  |

|  |                      |                       |                      |
|--|----------------------|-----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 1 / 129 (0.78%)<br>1 | 1 / 134 (0.75%)<br>1  | 0 / 226 (0.00%)<br>0 |
| <b>Blood and lymphatic system disorders</b>      |                      |                       |                      |
| <b>Anaemia</b>                                   |                      |                       |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1  | 1 / 226 (0.44%)<br>1 |
| <b>Leukopenia</b>                                |                      |                       |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0  | 2 / 226 (0.88%)<br>2 |
| <b>Lymphadenopathy</b>                           |                      |                       |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 2 / 134 (1.49%)<br>2  | 0 / 226 (0.00%)<br>0 |
| <b>Neutropenia</b>                               |                      |                       |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1  | 0 / 226 (0.00%)<br>0 |
| <b>Pancytopenia</b>                              |                      |                       |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0  | 1 / 226 (0.44%)<br>1 |
| <b>Thrombocytopenia</b>                          |                      |                       |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0  | 1 / 226 (0.44%)<br>1 |
| <b>Ear and labyrinth disorders</b>               |                      |                       |                      |
| <b>Ear pain</b>                                  |                      |                       |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1  | 0 / 226 (0.00%)<br>0 |
| <b>Tinnitus</b>                                  |                      |                       |                      |
| subjects affected / exposed<br>occurrences (all) | 1 / 129 (0.78%)<br>1 | 0 / 134 (0.00%)<br>0  | 1 / 226 (0.44%)<br>1 |
| <b>Tympanic membrane perforation</b>             |                      |                       |                      |
| subjects affected / exposed<br>occurrences (all) | 1 / 129 (0.78%)<br>1 | 0 / 134 (0.00%)<br>0  | 0 / 226 (0.00%)<br>0 |
| <b>Vertigo</b>                                   |                      |                       |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 5 / 134 (3.73%)<br>11 | 5 / 226 (2.21%)<br>9 |
| <b>Eye disorders</b>                             |                      |                       |                      |

|  |                      |                       |                        |
|--|----------------------|-----------------------|------------------------|
| Abnormal sensation in eye<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1  | 0 / 226 (0.00%)<br>0   |
| Astigmatism<br>subjects affected / exposed<br>occurrences (all)  | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0  | 1 / 226 (0.44%)<br>1   |
| Conjunctival haemorrhage<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0  | 1 / 226 (0.44%)<br>1   |
| Diplopia<br>subjects affected / exposed<br>occurrences (all)   | 2 / 129 (1.55%)<br>2 | 8 / 134 (5.97%)<br>12 | 12 / 226 (5.31%)<br>14 |
| Eye pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0  | 2 / 226 (0.88%)<br>2   |
| Eye swelling<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1  | 0 / 226 (0.00%)<br>0   |
| Lacrimation increased<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0  | 1 / 226 (0.44%)<br>1   |
| Optic atrophy<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1  | 0 / 226 (0.00%)<br>0   |
| Vision blurred<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1  | 1 / 226 (0.44%)<br>1   |
| Visual impairment<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1  | 1 / 226 (0.44%)<br>1   |
| Gastrointestinal disorders<br>Abdominal distension<br>subjects affected / exposed<br>occurrences (all) | 1 / 129 (0.78%)<br>1 | 0 / 134 (0.00%)<br>0  | 0 / 226 (0.00%)<br>0   |
| Abdominal pain   |                      |                       |                        |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 4 / 129 (3.10%) | 3 / 134 (2.24%) | 6 / 226 (2.65%) |
| occurrences (all)           | 7               | 4               | 8               |
| Abdominal pain upper        |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 4 / 134 (2.99%) | 3 / 226 (1.33%) |
| occurrences (all)           | 0               | 4               | 4               |
| Aphthous stomatitis         |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 2 / 226 (0.88%) |
| occurrences (all)           | 0               | 0               | 2               |
| Constipation                |                 |                 |                 |
| subjects affected / exposed | 2 / 129 (1.55%) | 3 / 134 (2.24%) | 1 / 226 (0.44%) |
| occurrences (all)           | 2               | 3               | 6               |
| Diarrhoea                   |                 |                 |                 |
| subjects affected / exposed | 3 / 129 (2.33%) | 1 / 134 (0.75%) | 4 / 226 (1.77%) |
| occurrences (all)           | 3               | 1               | 4               |
| Dyspepsia                   |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)           | 0               | 0               | 1               |
| Dysphagia                   |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Enteritis                   |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Enterocolitis               |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Flatulence                  |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)           | 0               | 0               | 1               |
| Food poisoning              |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)           | 1               | 1               | 0               |
| Frequent bowel movements    |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Gastritis                   |                 |                 |                 |

|                                 |                 |                 |                 |
|---------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed     | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)               | 0               | 1               | 0               |
| Gastroduodenitis                |                 |                 |                 |
| subjects affected / exposed     | 1 / 129 (0.78%) | 1 / 134 (0.75%) | 1 / 226 (0.44%) |
| occurrences (all)               | 1               | 1               | 1               |
| Gastroesophageal reflux disease |                 |                 |                 |
| subjects affected / exposed     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)               | 0               | 0               | 1               |
| Gingival bleeding               |                 |                 |                 |
| subjects affected / exposed     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)               | 0               | 0               | 0               |
| Gingivitis                      |                 |                 |                 |
| subjects affected / exposed     | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)               | 2               | 0               | 0               |
| Irritable bowel syndrome        |                 |                 |                 |
| subjects affected / exposed     | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)               | 1               | 0               | 0               |
| Lip dry                         |                 |                 |                 |
| subjects affected / exposed     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)               | 0               | 0               | 1               |
| Mouth ulceration                |                 |                 |                 |
| subjects affected / exposed     | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)               | 0               | 1               | 0               |
| Nausea                          |                 |                 |                 |
| subjects affected / exposed     | 1 / 129 (0.78%) | 7 / 134 (5.22%) | 5 / 226 (2.21%) |
| occurrences (all)               | 1               | 9               | 7               |
| Odynophagia                     |                 |                 |                 |
| subjects affected / exposed     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)               | 0               | 0               | 1               |
| Oesophagitis                    |                 |                 |                 |
| subjects affected / exposed     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)               | 0               | 0               | 0               |
| Oral pain                       |                 |                 |                 |
| subjects affected / exposed     | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)               | 1               | 0               | 0               |
| Pancreatic disorder             |                 |                 |                 |

|   |                      |                       |                        |
|---|----------------------|-----------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0  | 0 / 226 (0.00%)<br>0   |
| Periodontitis<br>subjects affected / exposed<br>occurrences (all)                                 | 1 / 129 (0.78%)<br>1 | 0 / 134 (0.00%)<br>0  | 1 / 226 (0.44%)<br>1   |
| Peritonitis<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0  | 1 / 226 (0.44%)<br>1   |
| Rectal fissure<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0  | 1 / 226 (0.44%)<br>1   |
| Salivary hypersecretion<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1  | 3 / 226 (1.33%)<br>3   |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0  | 0 / 226 (0.00%)<br>0   |
| Tooth disorder<br>subjects affected / exposed<br>occurrences (all)                                | 1 / 129 (0.78%)<br>1 | 0 / 134 (0.00%)<br>0  | 0 / 226 (0.00%)<br>0   |
| Toothache<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 129 (0.78%)<br>1 | 1 / 134 (0.75%)<br>1  | 0 / 226 (0.00%)<br>0   |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                      | 8 / 129 (6.20%)<br>9 | 8 / 134 (5.97%)<br>11 | 21 / 226 (9.29%)<br>32 |
| Hepatobiliary disorders<br>Biliary dyskinesia<br>subjects affected / exposed<br>occurrences (all) | 1 / 129 (0.78%)<br>1 | 0 / 134 (0.00%)<br>0  | 2 / 226 (0.88%)<br>2   |
| Hepatic cyst<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0  | 0 / 226 (0.00%)<br>0   |
| Hepatic steatosis<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0  | 1 / 226 (0.44%)<br>1   |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| Skin and subcutaneous tissue disorders |                 |                 |                 |
| Acne                                   |                 |                 |                 |
| subjects affected / exposed            | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)                      | 1               | 0               | 1               |
| Alopecia                               |                 |                 |                 |
| subjects affected / exposed            | 2 / 129 (1.55%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)                      | 2               | 0               | 1               |
| Dermatitis                             |                 |                 |                 |
| subjects affected / exposed            | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)                      | 0               | 1               | 0               |
| Dermatitis acneiform                   |                 |                 |                 |
| subjects affected / exposed            | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)                      | 0               | 0               | 1               |
| Dermatitis allergic                    |                 |                 |                 |
| subjects affected / exposed            | 2 / 129 (1.55%) | 2 / 134 (1.49%) | 2 / 226 (0.88%) |
| occurrences (all)                      | 3               | 2               | 2               |
| Dermatitis atopic                      |                 |                 |                 |
| subjects affected / exposed            | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)                      | 1               | 0               | 10              |
| Dermatitis contact                     |                 |                 |                 |
| subjects affected / exposed            | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 2 / 226 (0.88%) |
| occurrences (all)                      | 0               | 1               | 2               |
| Dermatitis diaper                      |                 |                 |                 |
| subjects affected / exposed            | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)                      | 0               | 1               | 0               |
| Dry skin                               |                 |                 |                 |
| subjects affected / exposed            | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)                      | 0               | 1               | 0               |
| Heat rash                              |                 |                 |                 |
| subjects affected / exposed            | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)                      | 1               | 0               | 0               |
| Ingrowing nail                         |                 |                 |                 |
| subjects affected / exposed            | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)                      | 0               | 0               | 0               |
| Onychomadesis                          |                 |                 |                 |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1 | 0 / 226 (0.00%)<br>0 |
| Papule   |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Pityriasis rosea                                 |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Pruritus   |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1 | 1 / 226 (0.44%)<br>1 |
| Rash   |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 4 / 129 (3.10%)<br>5 | 2 / 134 (1.49%)<br>2 | 3 / 226 (1.33%)<br>3 |
| Rash erythematous                                |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 1 / 129 (0.78%)<br>1 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Rash pruritic                                    |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Skin exfoliation                                 |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Solar dermatitis                                 |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1 | 0 / 226 (0.00%)<br>0 |
| Urticaria  |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Renal and urinary disorders                      |                      |                      |                      |
| Dysuria  |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Enuresis   |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 2 / 134 (1.49%)<br>2 | 0 / 226 (0.00%)<br>0 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Haematuria                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 2 / 226 (0.88%) |
| occurrences (all)                               | 0               | 0               | 2               |
| Incontinence                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)                               | 0               | 0               | 0               |
| Leukocyturia                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)                               | 0               | 0               | 1               |
| Nephropathy                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)                               | 1               | 0               | 0               |
| Nocturia  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)                               | 0               | 1               | 0               |
| Renal failure acute                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)                               | 0               | 0               | 0               |
| Urinary retention                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)                               | 0               | 1               | 0               |
| Endocrine disorders                             |                 |                 |                 |
| Goitre  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 2 / 226 (0.88%) |
| occurrences (all)                               | 0               | 1               | 2               |
| Hypothalamo-pituitary disorder                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)                               | 0               | 0               | 0               |
| Hypothyroidism                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 2 / 134 (1.49%) | 2 / 226 (0.88%) |
| occurrences (all)                               | 0               | 2               | 2               |
| Precocious puberty                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)                               | 0               | 0               | 1               |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| Ankle deformity             |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Arthralgia                  |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 2 / 134 (1.49%) | 0 / 226 (0.00%) |
| occurrences (all)           | 1               | 2               | 0               |
| Arthritis reactive          |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)           | 0               | 0               | 1               |
| Back pain                   |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)           | 1               | 0               | 3               |
| Chest wall mass             |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Elbow deformity             |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)           | 0               | 0               | 1               |
| Foot deformity              |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Groin pain                  |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)           | 0               | 0               | 1               |
| Haemarthrosis               |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Joint swelling              |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Myalgia                     |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Neck pain                   |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)           | 0               | 0               | 1               |

|  |                      |                      |                       |
|--|----------------------|----------------------|-----------------------|
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)        | 1 / 129 (0.78%)<br>2 | 1 / 134 (0.75%)<br>1 | 1 / 226 (0.44%)<br>1  |
| Rhabdomyolysis<br>subjects affected / exposed<br>occurrences (all)           | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0  |
| <b>Infections and infestations</b>   |                      |                      |                       |
| Abscess limb<br>subjects affected / exposed<br>occurrences (all)             | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1 | 0 / 226 (0.00%)<br>0  |
| Acute sinusitis<br>subjects affected / exposed<br>occurrences (all)          | 1 / 129 (0.78%)<br>2 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0  |
| Acute tonsillitis<br>subjects affected / exposed<br>occurrences (all)        | 1 / 129 (0.78%)<br>1 | 1 / 134 (0.75%)<br>2 | 6 / 226 (2.65%)<br>7  |
| Appendicitis<br>subjects affected / exposed<br>occurrences (all)             | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)               | 7 / 129 (5.43%)<br>7 | 5 / 134 (3.73%)<br>5 | 8 / 226 (3.54%)<br>10 |
| Bronchopneumonia<br>subjects affected / exposed<br>occurrences (all)         | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0  |
| Bullous impetigo<br>subjects affected / exposed<br>occurrences (all)         | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1 | 1 / 226 (0.44%)<br>1  |
| Conjunctivitis bacterial<br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>2 | 0 / 226 (0.00%)<br>0  |
| Cystitis<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 129 (0.78%)<br>1 | 2 / 134 (1.49%)<br>2 | 0 / 226 (0.00%)<br>0  |
| Ear infection  |                      |                      |                       |

|                                  |                 |                 |                 |
|----------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed      | 3 / 129 (2.33%) | 0 / 134 (0.00%) | 6 / 226 (2.65%) |
| occurrences (all)                | 4               | 0               | 6               |
| Febrile infection                |                 |                 |                 |
| subjects affected / exposed      | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)                | 0               | 1               | 0               |
| Fungal skin infection            |                 |                 |                 |
| subjects affected / exposed      | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 2 / 226 (0.88%) |
| occurrences (all)                | 0               | 0               | 2               |
| Gastroenteritis                  |                 |                 |                 |
| subjects affected / exposed      | 1 / 129 (0.78%) | 3 / 134 (2.24%) | 8 / 226 (3.54%) |
| occurrences (all)                | 1               | 4               | 9               |
| Gastroenteritis viral            |                 |                 |                 |
| subjects affected / exposed      | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 2 / 226 (0.88%) |
| occurrences (all)                | 0               | 1               | 2               |
| Gastrointestinal viral infection |                 |                 |                 |
| subjects affected / exposed      | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)                | 0               | 0               | 1               |
| Helicobacter infection           |                 |                 |                 |
| subjects affected / exposed      | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)                | 0               | 1               | 0               |
| Herpes simplex                   |                 |                 |                 |
| subjects affected / exposed      | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)                | 1               | 0               | 0               |
| Hordeolum                        |                 |                 |                 |
| subjects affected / exposed      | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 0 / 226 (0.00%) |
| occurrences (all)                | 0               | 0               | 0               |
| Impetigo                         |                 |                 |                 |
| subjects affected / exposed      | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 2 / 226 (0.88%) |
| occurrences (all)                | 0               | 0               | 2               |
| Infected bites                   |                 |                 |                 |
| subjects affected / exposed      | 0 / 129 (0.00%) | 1 / 134 (0.75%) | 0 / 226 (0.00%) |
| occurrences (all)                | 0               | 1               | 0               |
| Infection                        |                 |                 |                 |
| subjects affected / exposed      | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%) |
| occurrences (all)                | 0               | 0               | 1               |
| Influenza                        |                 |                 |                 |

|  |                   |                   |                   |
|--|-------------------|-------------------|-------------------|
| subjects affected / exposed              | 1 / 129 (0.78%)   | 4 / 134 (2.99%)   | 6 / 226 (2.65%)   |
| occurrences (all)                        | 2                 | 9                 | 14                |
| <b>Laryngitis</b>                        |                   |                   |                   |
| subjects affected / exposed              | 0 / 129 (0.00%)   | 0 / 134 (0.00%)   | 2 / 226 (0.88%)   |
| occurrences (all)                        | 0                 | 0                 | 2                 |
| <b>Lower respiratory tract infection</b> |                   |                   |                   |
| subjects affected / exposed              | 0 / 129 (0.00%)   | 1 / 134 (0.75%)   | 0 / 226 (0.00%)   |
| occurrences (all)                        | 0                 | 1                 | 0                 |
| <b>Mastitis</b>                          |                   |                   |                   |
| subjects affected / exposed              | 0 / 129 (0.00%)   | 0 / 134 (0.00%)   | 0 / 226 (0.00%)   |
| occurrences (all)                        | 0                 | 0                 | 0                 |
| <b>Nasopharyngitis</b>                   |                   |                   |                   |
| subjects affected / exposed              | 15 / 129 (11.63%) | 15 / 134 (11.19%) | 31 / 226 (13.72%) |
| occurrences (all)                        | 23                | 22                | 43                |
| <b>Onychomycosis</b>                     |                   |                   |                   |
| subjects affected / exposed              | 1 / 129 (0.78%)   | 0 / 134 (0.00%)   | 0 / 226 (0.00%)   |
| occurrences (all)                        | 1                 | 0                 | 0                 |
| <b>Oral herpes</b>                       |                   |                   |                   |
| subjects affected / exposed              | 0 / 129 (0.00%)   | 2 / 134 (1.49%)   | 1 / 226 (0.44%)   |
| occurrences (all)                        | 0                 | 2                 | 1                 |
| <b>Otitis externa</b>                    |                   |                   |                   |
| subjects affected / exposed              | 0 / 129 (0.00%)   | 1 / 134 (0.75%)   | 0 / 226 (0.00%)   |
| occurrences (all)                        | 0                 | 1                 | 0                 |
| <b>Otitis media</b>                      |                   |                   |                   |
| subjects affected / exposed              | 1 / 129 (0.78%)   | 2 / 134 (1.49%)   | 2 / 226 (0.88%)   |
| occurrences (all)                        | 1                 | 2                 | 2                 |
| <b>Otitis media acute</b>                |                   |                   |                   |
| subjects affected / exposed              | 0 / 129 (0.00%)   | 1 / 134 (0.75%)   | 0 / 226 (0.00%)   |
| occurrences (all)                        | 0                 | 1                 | 0                 |
| <b>Parasitic gastroenteritis</b>         |                   |                   |                   |
| subjects affected / exposed              | 0 / 129 (0.00%)   | 0 / 134 (0.00%)   | 1 / 226 (0.44%)   |
| occurrences (all)                        | 0                 | 0                 | 1                 |
| <b>Paronychia</b>                        |                   |                   |                   |
| subjects affected / exposed              | 0 / 129 (0.00%)   | 0 / 134 (0.00%)   | 0 / 226 (0.00%)   |
| occurrences (all)                        | 0                 | 0                 | 0                 |
| <b>Pharyngitis</b>                       |                   |                   |                   |

|                                   |                 |                 |                  |
|-----------------------------------|-----------------|-----------------|------------------|
| subjects affected / exposed       | 9 / 129 (6.98%) | 9 / 134 (6.72%) | 10 / 226 (4.42%) |
| occurrences (all)                 | 9               | 10              | 14               |
| Pharyngotonsillitis               |                 |                 |                  |
| subjects affected / exposed       | 1 / 129 (0.78%) | 2 / 134 (1.49%) | 3 / 226 (1.33%)  |
| occurrences (all)                 | 1               | 2               | 3                |
| Pneumonia                         |                 |                 |                  |
| subjects affected / exposed       | 2 / 129 (1.55%) | 1 / 134 (0.75%) | 2 / 226 (0.88%)  |
| occurrences (all)                 | 2               | 1               | 2                |
| Pulmonary tuberculosis            |                 |                 |                  |
| subjects affected / exposed       | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%)  |
| occurrences (all)                 | 0               | 0               | 1                |
| Pulpitis dental                   |                 |                 |                  |
| subjects affected / exposed       | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%)  |
| occurrences (all)                 | 0               | 0               | 1                |
| Respiratory tract infection       |                 |                 |                  |
| subjects affected / exposed       | 7 / 129 (5.43%) | 7 / 134 (5.22%) | 13 / 226 (5.75%) |
| occurrences (all)                 | 7               | 10              | 28               |
| Respiratory tract infection viral |                 |                 |                  |
| subjects affected / exposed       | 3 / 129 (2.33%) | 2 / 134 (1.49%) | 6 / 226 (2.65%)  |
| occurrences (all)                 | 3               | 3               | 14               |
| Rhinitis                          |                 |                 |                  |
| subjects affected / exposed       | 7 / 129 (5.43%) | 4 / 134 (2.99%) | 5 / 226 (2.21%)  |
| occurrences (all)                 | 7               | 5               | 7                |
| Sinusitis                         |                 |                 |                  |
| subjects affected / exposed       | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%)  |
| occurrences (all)                 | 0               | 0               | 1                |
| Subcutaneous abscess              |                 |                 |                  |
| subjects affected / exposed       | 0 / 129 (0.00%) | 0 / 134 (0.00%) | 1 / 226 (0.44%)  |
| occurrences (all)                 | 0               | 0               | 1                |
| Tinea infection                   |                 |                 |                  |
| subjects affected / exposed       | 1 / 129 (0.78%) | 0 / 134 (0.00%) | 0 / 226 (0.00%)  |
| occurrences (all)                 | 1               | 0               | 0                |
| Tonsillitis                       |                 |                 |                  |
| subjects affected / exposed       | 4 / 129 (3.10%) | 2 / 134 (1.49%) | 4 / 226 (1.77%)  |
| occurrences (all)                 | 4               | 2               | 5                |
| Tracheitis                        |                 |                 |                  |

|   |                      |                      |                        |
|---|----------------------|----------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)  | 1 / 129 (0.78%)<br>1 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0   |
| Tracheobronchitis<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1   |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                       | 5 / 129 (3.88%)<br>8 | 6 / 134 (4.48%)<br>8 | 10 / 226 (4.42%)<br>18 |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                                 | 1 / 129 (0.78%)<br>1 | 0 / 134 (0.00%)<br>0 | 4 / 226 (1.77%)<br>4   |
| Urinary tract infection bacterial<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 129 (0.78%)<br>1 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0   |
| Varicella<br>subjects affected / exposed<br>occurrences (all)   | 2 / 129 (1.55%)<br>2 | 2 / 134 (1.49%)<br>2 | 2 / 226 (0.88%)<br>2   |
| Viral infection<br>subjects affected / exposed<br>occurrences (all)   | 6 / 129 (4.65%)<br>7 | 5 / 134 (3.73%)<br>5 | 12 / 226 (5.31%)<br>13 |
| Viral pharyngitis<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1   |
| Viral rash<br>subjects affected / exposed<br>occurrences (all)  | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1   |
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                 | 3 / 129 (2.33%)<br>6 | 5 / 134 (3.73%)<br>6 | 7 / 226 (3.10%)<br>9   |
| Vulvitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0   |
| Metabolism and nutrition disorders<br>Appetite disorder<br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 2 / 134 (1.49%)<br>2 | 0 / 226 (0.00%)<br>0   |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 1 / 129 (0.78%)<br>1 | 6 / 134 (4.48%)<br>8 | 2 / 226 (0.88%)<br>2 |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)        | 1 / 129 (0.78%)<br>1 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Feeding disorder<br>subjects affected / exposed<br>occurrences (all)   | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)     | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 0 / 226 (0.00%)<br>0 |
| Hyperphagia<br>subjects affected / exposed<br>occurrences (all)        | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1 | 1 / 226 (0.44%)<br>1 |
| Increased appetite<br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1 | 1 / 226 (0.44%)<br>1 |
| Iron deficiency<br>subjects affected / exposed<br>occurrences (all)    | 0 / 129 (0.00%)<br>0 | 1 / 134 (0.75%)<br>1 | 0 / 226 (0.00%)<br>0 |
| Obesity<br>subjects affected / exposed<br>occurrences (all)            | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |
| Weight gain poor<br>subjects affected / exposed<br>occurrences (all)   | 0 / 129 (0.00%)<br>0 | 0 / 134 (0.00%)<br>0 | 1 / 226 (0.44%)<br>1 |

|  |                                  |  |  |
|--|----------------------------------|--|--|
| <b>Non-serious adverse events</b>  | Part III-V - ESL x<br>Safety Set |  |  |
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed  | 96 / 152 (63.16%)                |  |  |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps)<br>Oral papilloma<br>subjects affected / exposed<br>occurrences (all) | 0 / 152 (0.00%)<br>0             |  |  |
| Sebaceous adenoma  |                                  |  |  |

|   |                      |  |  |
|---|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                                | 0 / 152 (0.00%)<br>0 |  |  |
| Skin papilloma<br>subjects affected / exposed<br>occurrences (all)              | 1 / 152 (0.66%)<br>1 |  |  |
| Vascular disorders  |                      |  |  |
| Haematoma<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 152 (0.00%)<br>0 |  |  |
| Hypertension<br>subjects affected / exposed<br>occurrences (all)                | 0 / 152 (0.00%)<br>0 |  |  |
| Phlebitis<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 152 (0.00%)<br>0 |  |  |
| Systolic hypertension<br>subjects affected / exposed<br>occurrences (all)       | 1 / 152 (0.66%)<br>1 |  |  |
| Surgical and medical procedures   |                      |  |  |
| Adenoidectomy<br>subjects affected / exposed<br>occurrences (all)               | 1 / 152 (0.66%)<br>1 |  |  |
| Brain operation<br>subjects affected / exposed<br>occurrences (all)             | 0 / 152 (0.00%)<br>0 |  |  |
| Plastic surgery to the face<br>subjects affected / exposed<br>occurrences (all) | 0 / 152 (0.00%)<br>0 |  |  |
| Suture insertion<br>subjects affected / exposed<br>occurrences (all)            | 0 / 152 (0.00%)<br>0 |  |  |
| Tenotomy<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 152 (0.00%)<br>0 |  |  |
| Tooth extraction  |                      |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                          | 0 / 152 (0.00%) |  |  |
| occurrences (all)                                    | 0               |  |  |
| General disorders and administration site conditions |                 |  |  |
| Asthenia   |                 |  |  |
| subjects affected / exposed                          | 2 / 152 (1.32%) |  |  |
| occurrences (all)                                    | 3               |  |  |
| Chest pain   |                 |  |  |
| subjects affected / exposed                          | 1 / 152 (0.66%) |  |  |
| occurrences (all)                                    | 1               |  |  |
| Device malfunction                                   |                 |  |  |
| subjects affected / exposed                          | 0 / 152 (0.00%) |  |  |
| occurrences (all)                                    | 0               |  |  |
| Face oedema  |                 |  |  |
| subjects affected / exposed                          | 0 / 152 (0.00%) |  |  |
| occurrences (all)                                    | 0               |  |  |
| Fatigue  |                 |  |  |
| subjects affected / exposed                          | 3 / 152 (1.97%) |  |  |
| occurrences (all)                                    | 5               |  |  |
| Feeling hot  |                 |  |  |
| subjects affected / exposed                          | 0 / 152 (0.00%) |  |  |
| occurrences (all)                                    | 0               |  |  |
| Gait disturbance                                     |                 |  |  |
| subjects affected / exposed                          | 0 / 152 (0.00%) |  |  |
| occurrences (all)                                    | 0               |  |  |
| Hyperthermia   |                 |  |  |
| subjects affected / exposed                          | 1 / 152 (0.66%) |  |  |
| occurrences (all)                                    | 1               |  |  |
| Irritability   |                 |  |  |
| subjects affected / exposed                          | 1 / 152 (0.66%) |  |  |
| occurrences (all)                                    | 2               |  |  |
| Malaise  |                 |  |  |
| subjects affected / exposed                          | 0 / 152 (0.00%) |  |  |
| occurrences (all)                                    | 0               |  |  |
| Oedema   |                 |  |  |

|   |                        |  |  |
|---|------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)  | 0 / 152 (0.00%)<br>0   |  |  |
| Pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 152 (0.00%)<br>0   |  |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)   | 14 / 152 (9.21%)<br>21 |  |  |
| Sluggishness<br>subjects affected / exposed<br>occurrences (all)  | 0 / 152 (0.00%)<br>0   |  |  |
| Thirst<br>subjects affected / exposed<br>occurrences (all)  | 0 / 152 (0.00%)<br>0   |  |  |
| Immune system disorders<br>Allergy to arthropod bite<br>subjects affected / exposed<br>occurrences (all)      | 0 / 152 (0.00%)<br>0   |  |  |
| Drug hypersensitivity<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 152 (0.00%)<br>0   |  |  |
| Hypersensitivity<br>subjects affected / exposed<br>occurrences (all)  | 0 / 152 (0.00%)<br>0   |  |  |
| Immunodeficiency<br>subjects affected / exposed<br>occurrences (all)  | 0 / 152 (0.00%)<br>0   |  |  |
| Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)  | 0 / 152 (0.00%)<br>0   |  |  |
| Reproductive system and breast disorders<br>Dysmenorrhoea<br>subjects affected / exposed<br>occurrences (all) | 1 / 152 (0.66%)<br>2   |  |  |
| Epididymal cyst   |                        |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 152 (0.66%) |  |  |
| occurrences (all)                               | 1               |  |  |
| Labia enlarged                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Menstruation irregular                          |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Pelvic pain                                     |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Polycystic ovaries                              |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Vaginal discharge                               |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Asthma  |                 |  |  |
| subjects affected / exposed                     | 2 / 152 (1.32%) |  |  |
| occurrences (all)                               | 3               |  |  |
| Bronchospasm                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 152 (0.66%) |  |  |
| occurrences (all)                               | 1               |  |  |
| Cough   |                 |  |  |
| subjects affected / exposed                     | 4 / 152 (2.63%) |  |  |
| occurrences (all)                               | 5               |  |  |
| Epistaxis                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Laryngospasm                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 152 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Nasal discomfort                                |                 |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                           | 0 / 152 (0.00%)<br>0 |  |  |
| Nasal obstruction<br>subjects affected / exposed<br>occurrences (all)      | 0 / 152 (0.00%)<br>0 |  |  |
| Nasal septum deviation<br>subjects affected / exposed<br>occurrences (all) | 0 / 152 (0.00%)<br>0 |  |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)     | 3 / 152 (1.97%)<br>7 |  |  |
| Respiratory disorder<br>subjects affected / exposed<br>occurrences (all)   | 0 / 152 (0.00%)<br>0 |  |  |
| Rhinitis allergic<br>subjects affected / exposed<br>occurrences (all)      | 1 / 152 (0.66%)<br>1 |  |  |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)            | 0 / 152 (0.00%)<br>0 |  |  |
| Tonsillar hypertrophy<br>subjects affected / exposed<br>occurrences (all)  | 0 / 152 (0.00%)<br>0 |  |  |
| Tonsillar inflammation<br>subjects affected / exposed<br>occurrences (all) | 0 / 152 (0.00%)<br>0 |  |  |
| Vasomotor rhinitis<br>subjects affected / exposed<br>occurrences (all)     | 1 / 152 (0.66%)<br>1 |  |  |
| Psychiatric disorders  |                      |  |  |
| Abnormal behaviour<br>subjects affected / exposed<br>occurrences (all)     | 1 / 152 (0.66%)<br>1 |  |  |
| Affect lability<br>subjects affected / exposed<br>occurrences (all)        | 1 / 152 (0.66%)<br>1 |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| Agitation                                |                 |  |  |
| subjects affected / exposed              | 0 / 152 (0.00%) |  |  |
| occurrences (all)                        | 0               |  |  |
| Anxiety                                  |                 |  |  |
| subjects affected / exposed              | 0 / 152 (0.00%) |  |  |
| occurrences (all)                        | 0               |  |  |
| Apathy                                   |                 |  |  |
| subjects affected / exposed              | 0 / 152 (0.00%) |  |  |
| occurrences (all)                        | 0               |  |  |
| Attention deficit/Hyperactivity disorder |                 |  |  |
| subjects affected / exposed              | 1 / 152 (0.66%) |  |  |
| occurrences (all)                        | 1               |  |  |
| Bradyphrenia                             |                 |  |  |
| subjects affected / exposed              | 0 / 152 (0.00%) |  |  |
| occurrences (all)                        | 0               |  |  |
| Bruxism                                  |                 |  |  |
| subjects affected / exposed              | 0 / 152 (0.00%) |  |  |
| occurrences (all)                        | 0               |  |  |
| Confusional state                        |                 |  |  |
| subjects affected / exposed              | 0 / 152 (0.00%) |  |  |
| occurrences (all)                        | 0               |  |  |
| Depressed mood                           |                 |  |  |
| subjects affected / exposed              | 0 / 152 (0.00%) |  |  |
| occurrences (all)                        | 0               |  |  |
| Disorientation                           |                 |  |  |
| subjects affected / exposed              | 0 / 152 (0.00%) |  |  |
| occurrences (all)                        | 0               |  |  |
| Dyslogia                                 |                 |  |  |
| subjects affected / exposed              | 0 / 152 (0.00%) |  |  |
| occurrences (all)                        | 0               |  |  |
| Dysthymic disorder                       |                 |  |  |
| subjects affected / exposed              | 0 / 152 (0.00%) |  |  |
| occurrences (all)                        | 0               |  |  |
| Emotional distress                       |                 |  |  |

|                               |                 |  |  |
|-------------------------------|-----------------|--|--|
| subjects affected / exposed   | 1 / 152 (0.66%) |  |  |
| occurrences (all)             | 2               |  |  |
| Encopresis                    |                 |  |  |
| subjects affected / exposed   | 1 / 152 (0.66%) |  |  |
| occurrences (all)             | 2               |  |  |
| Inappropriate affect          |                 |  |  |
| subjects affected / exposed   | 0 / 152 (0.00%) |  |  |
| occurrences (all)             | 0               |  |  |
| Initial insomnia              |                 |  |  |
| subjects affected / exposed   | 1 / 152 (0.66%) |  |  |
| occurrences (all)             | 1               |  |  |
| Insomnia                      |                 |  |  |
| subjects affected / exposed   | 1 / 152 (0.66%) |  |  |
| occurrences (all)             | 2               |  |  |
| Listless                      |                 |  |  |
| subjects affected / exposed   | 0 / 152 (0.00%) |  |  |
| occurrences (all)             | 0               |  |  |
| Mood altered                  |                 |  |  |
| subjects affected / exposed   | 1 / 152 (0.66%) |  |  |
| occurrences (all)             | 1               |  |  |
| Mood swings                   |                 |  |  |
| subjects affected / exposed   | 0 / 152 (0.00%) |  |  |
| occurrences (all)             | 0               |  |  |
| Nervousness                   |                 |  |  |
| subjects affected / exposed   | 1 / 152 (0.66%) |  |  |
| occurrences (all)             | 1               |  |  |
| Obsessive-compulsive disorder |                 |  |  |
| subjects affected / exposed   | 0 / 152 (0.00%) |  |  |
| occurrences (all)             | 0               |  |  |
| Panic attack                  |                 |  |  |
| subjects affected / exposed   | 0 / 152 (0.00%) |  |  |
| occurrences (all)             | 0               |  |  |
| Restlessness                  |                 |  |  |
| subjects affected / exposed   | 0 / 152 (0.00%) |  |  |
| occurrences (all)             | 0               |  |  |
| Sleep disorder                |                 |  |  |

|   |                      |  |  |
|---|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)  | 1 / 152 (0.66%)<br>1 |  |  |
| Sleep talking<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 152 (0.00%)<br>0 |  |  |
| Somatoform disorder<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 152 (0.66%)<br>1 |  |  |
| <b>Investigations</b>   |                      |  |  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)        | 1 / 152 (0.66%)<br>1 |  |  |
| Aspartate aminotransferase<br>increased<br>subjects affected / exposed<br>occurrences (all)   | 1 / 152 (0.66%)<br>1 |  |  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)      | 0 / 152 (0.00%)<br>0 |  |  |
| Blood bicarbonate decreased<br>subjects affected / exposed<br>occurrences (all)               | 1 / 152 (0.66%)<br>1 |  |  |
| Blood calcium decreased<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 152 (0.00%)<br>0 |  |  |
| Blood creatine phosphokinase<br>increased<br>subjects affected / exposed<br>occurrences (all) | 5 / 152 (3.29%)<br>5 |  |  |
| Blood glucose decreased<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 152 (0.00%)<br>0 |  |  |
| Blood lactate dehydrogenase<br>increased<br>subjects affected / exposed<br>occurrences (all)  | 2 / 152 (1.32%)<br>2 |  |  |
| Blood thyroid stimulating hormone<br>increased  |                      |  |  |

|   |                        |  |  |
|---|------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)  | 0 / 152 (0.00%)<br>0   |  |  |
| Blood triglycerides increased<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 152 (0.66%)<br>1   |  |  |
| Body temperature increased<br>subjects affected / exposed<br>occurrences (all)                      | 2 / 152 (1.32%)<br>2   |  |  |
| Breath sounds abnormal<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 152 (0.00%)<br>0   |  |  |
| Ecg p wave inverted<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 152 (0.00%)<br>0   |  |  |
| Electrocardiogram pr shortened<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 152 (0.66%)<br>1   |  |  |
| Electrocardiogram pr prolongation<br>subjects affected / exposed<br>occurrences (all)               | 0 / 152 (0.00%)<br>0   |  |  |
| Electrocardiogram qt prolonged<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 152 (0.66%)<br>1   |  |  |
| Electrocardiogram repolarisation<br>abnormality<br>subjects affected / exposed<br>occurrences (all) | 0 / 152 (0.00%)<br>0   |  |  |
| Eosinophil count increased<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 152 (0.66%)<br>1   |  |  |
| Gamma-glutamyltransferase<br>increased<br>subjects affected / exposed<br>occurrences (all)          | 10 / 152 (6.58%)<br>10 |  |  |
| Haemoglobin decreased   |                        |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                                     | 2 / 152 (1.32%)<br>2 |  |  |
| Hepatic enzyme increased<br>subjects affected / exposed<br>occurrences (all)         | 1 / 152 (0.66%)<br>1 |  |  |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)         | 1 / 152 (0.66%)<br>1 |  |  |
| Platelet count increased<br>subjects affected / exposed<br>occurrences (all)         | 0 / 152 (0.00%)<br>0 |  |  |
| Positive rombergism<br>subjects affected / exposed<br>occurrences (all)              | 0 / 152 (0.00%)<br>0 |  |  |
| Rheumatoid factor increased<br>subjects affected / exposed<br>occurrences (all)      | 0 / 152 (0.00%)<br>0 |  |  |
| Thyroxine decreased<br>subjects affected / exposed<br>occurrences (all)              | 0 / 152 (0.00%)<br>0 |  |  |
| Thyroxine increased<br>subjects affected / exposed<br>occurrences (all)              | 0 / 152 (0.00%)<br>0 |  |  |
| Transaminases increased<br>subjects affected / exposed<br>occurrences (all)          | 1 / 152 (0.66%)<br>2 |  |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                 | 3 / 152 (1.97%)<br>3 |  |  |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 152 (0.00%)<br>0 |  |  |
| White blood cell count increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 152 (0.66%)<br>1 |  |  |
| Injury, poisoning and procedural   |                      |  |  |

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| complications               |                 |  |  |  |
| Arthropod bite              |                 |  |  |  |
| subjects affected / exposed | 1 / 152 (0.66%) |  |  |  |
| occurrences (all)           | 1               |  |  |  |
| Clavicle fracture           |                 |  |  |  |
| subjects affected / exposed | 1 / 152 (0.66%) |  |  |  |
| occurrences (all)           | 1               |  |  |  |
| Concussion                  |                 |  |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |  |
| occurrences (all)           | 0               |  |  |  |
| Contusion                   |                 |  |  |  |
| subjects affected / exposed | 2 / 152 (1.32%) |  |  |  |
| occurrences (all)           | 2               |  |  |  |
| Drug toxicity               |                 |  |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |  |
| occurrences (all)           | 0               |  |  |  |
| Excoriation                 |                 |  |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |  |
| occurrences (all)           | 0               |  |  |  |
| Face injury                 |                 |  |  |  |
| subjects affected / exposed | 1 / 152 (0.66%) |  |  |  |
| occurrences (all)           | 1               |  |  |  |
| Fall                        |                 |  |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |  |
| occurrences (all)           | 0               |  |  |  |
| Foot fracture               |                 |  |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |  |
| occurrences (all)           | 0               |  |  |  |
| Forearm fracture            |                 |  |  |  |
| subjects affected / exposed | 1 / 152 (0.66%) |  |  |  |
| occurrences (all)           | 1               |  |  |  |
| Hand fracture               |                 |  |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |  |
| occurrences (all)           | 0               |  |  |  |
| Head injury                 |                 |  |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| <b>Injury</b>               |                 |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| <b>Joint injury</b>         |                 |  |  |
| subjects affected / exposed | 1 / 152 (0.66%) |  |  |
| occurrences (all)           | 1               |  |  |
| <b>Laceration</b>           |                 |  |  |
| subjects affected / exposed | 1 / 152 (0.66%) |  |  |
| occurrences (all)           | 1               |  |  |
| <b>Ligament sprain</b>      |                 |  |  |
| subjects affected / exposed | 1 / 152 (0.66%) |  |  |
| occurrences (all)           | 1               |  |  |
| <b>Limb injury</b>          |                 |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| <b>Lip injury</b>           |                 |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| <b>Overdose</b>             |                 |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| <b>Poisoning</b>            |                 |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| <b>Radius fracture</b>      |                 |  |  |
| subjects affected / exposed | 1 / 152 (0.66%) |  |  |
| occurrences (all)           | 2               |  |  |
| <b>Skin injury</b>          |                 |  |  |
| subjects affected / exposed | 1 / 152 (0.66%) |  |  |
| occurrences (all)           | 1               |  |  |
| <b>Skin wound</b>           |                 |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| <b>Soft tissue injury</b>   |                 |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                               | 1 / 152 (0.66%)<br>1 |  |  |
| Thermal burn<br>subjects affected / exposed<br>occurrences (all)               | 1 / 152 (0.66%)<br>2 |  |  |
| Tibia fracture<br>subjects affected / exposed<br>occurrences (all)             | 2 / 152 (1.32%)<br>2 |  |  |
| Tooth fracture<br>subjects affected / exposed<br>occurrences (all)             | 0 / 152 (0.00%)<br>0 |  |  |
| Tooth injury<br>subjects affected / exposed<br>occurrences (all)               | 0 / 152 (0.00%)<br>0 |  |  |
| Toxicity to various agents<br>subjects affected / exposed<br>occurrences (all) | 1 / 152 (0.66%)<br>1 |  |  |
| Traumatic haematoma<br>subjects affected / exposed<br>occurrences (all)        | 1 / 152 (0.66%)<br>1 |  |  |
| Upper limb fracture<br>subjects affected / exposed<br>occurrences (all)        | 0 / 152 (0.00%)<br>0 |  |  |
| Wound<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 152 (0.00%)<br>0 |  |  |
| Wrist fracture<br>subjects affected / exposed<br>occurrences (all)             | 0 / 152 (0.00%)<br>0 |  |  |
| Congenital, familial and genetic disorders                                     |                      |  |  |
| Atrial septal defect<br>subjects affected / exposed<br>occurrences (all)       | 0 / 152 (0.00%)<br>0 |  |  |
| Phimosi  |                      |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 152 (0.00%)<br>0 |  |  |
| Cardiac disorders                                |                      |  |  |
| Arrhythmia                                       |                      |  |  |
| subjects affected / exposed                      | 1 / 152 (0.66%)      |  |  |
| occurrences (all)                                | 1                    |  |  |
| Bradyarrhythmia                                  |                      |  |  |
| subjects affected / exposed                      | 1 / 152 (0.66%)      |  |  |
| occurrences (all)                                | 1                    |  |  |
| Tachycardia                                      |                      |  |  |
| subjects affected / exposed                      | 0 / 152 (0.00%)      |  |  |
| occurrences (all)                                | 0                    |  |  |
| Tricuspid valve incompetence                     |                      |  |  |
| subjects affected / exposed                      | 1 / 152 (0.66%)      |  |  |
| occurrences (all)                                | 1                    |  |  |
| Wolff-parkinson-white syndrome                   |                      |  |  |
| subjects affected / exposed                      | 1 / 152 (0.66%)      |  |  |
| occurrences (all)                                | 1                    |  |  |
| Nervous system disorders                         |                      |  |  |
| Ataxia   |                      |  |  |
| subjects affected / exposed                      | 0 / 152 (0.00%)      |  |  |
| occurrences (all)                                | 0                    |  |  |
| Balance disorder                                 |                      |  |  |
| subjects affected / exposed                      | 0 / 152 (0.00%)      |  |  |
| occurrences (all)                                | 0                    |  |  |
| Cerebellar ataxia                                |                      |  |  |
| subjects affected / exposed                      | 0 / 152 (0.00%)      |  |  |
| occurrences (all)                                | 0                    |  |  |
| Cerebrovascular disorder                         |                      |  |  |
| subjects affected / exposed                      | 0 / 152 (0.00%)      |  |  |
| occurrences (all)                                | 0                    |  |  |
| Circadian rhythm sleep disorder                  |                      |  |  |
| subjects affected / exposed                      | 1 / 152 (0.66%)      |  |  |
| occurrences (all)                                | 2                    |  |  |
| Cognitive disorder                               |                      |  |  |

|                                  |                   |  |  |
|----------------------------------|-------------------|--|--|
| subjects affected / exposed      | 2 / 152 (1.32%)   |  |  |
| occurrences (all)                | 2                 |  |  |
| Convulsion                       |                   |  |  |
| subjects affected / exposed      | 18 / 152 (11.84%) |  |  |
| occurrences (all)                | 25                |  |  |
| Coordination abnormal            |                   |  |  |
| subjects affected / exposed      | 0 / 152 (0.00%)   |  |  |
| occurrences (all)                | 0                 |  |  |
| Depressed level of consciousness |                   |  |  |
| subjects affected / exposed      | 1 / 152 (0.66%)   |  |  |
| occurrences (all)                | 2                 |  |  |
| Dizziness                        |                   |  |  |
| subjects affected / exposed      | 2 / 152 (1.32%)   |  |  |
| occurrences (all)                | 2                 |  |  |
| Epilepsy                         |                   |  |  |
| subjects affected / exposed      | 0 / 152 (0.00%)   |  |  |
| occurrences (all)                | 0                 |  |  |
| Head titubation                  |                   |  |  |
| subjects affected / exposed      | 0 / 152 (0.00%)   |  |  |
| occurrences (all)                | 0                 |  |  |
| Headache                         |                   |  |  |
| subjects affected / exposed      | 12 / 152 (7.89%)  |  |  |
| occurrences (all)                | 18                |  |  |
| Hypotonia                        |                   |  |  |
| subjects affected / exposed      | 0 / 152 (0.00%)   |  |  |
| occurrences (all)                | 0                 |  |  |
| Intention tremor                 |                   |  |  |
| subjects affected / exposed      | 1 / 152 (0.66%)   |  |  |
| occurrences (all)                | 1                 |  |  |
| Intracranial haematoma           |                   |  |  |
| subjects affected / exposed      | 1 / 152 (0.66%)   |  |  |
| occurrences (all)                | 1                 |  |  |
| Lethargy                         |                   |  |  |
| subjects affected / exposed      | 0 / 152 (0.00%)   |  |  |
| occurrences (all)                | 0                 |  |  |
| Memory impairment                |                   |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                    | 0 / 152 (0.00%) |  |  |
| occurrences (all)                              | 0               |  |  |
| Mental impairment                              |                 |  |  |
| subjects affected / exposed                    | 0 / 152 (0.00%) |  |  |
| occurrences (all)                              | 0               |  |  |
| Migraine                                       |                 |  |  |
| subjects affected / exposed                    | 0 / 152 (0.00%) |  |  |
| occurrences (all)                              | 0               |  |  |
| Nystagmus                                      |                 |  |  |
| subjects affected / exposed                    | 0 / 152 (0.00%) |  |  |
| occurrences (all)                              | 0               |  |  |
| Paraesthesia                                   |                 |  |  |
| subjects affected / exposed                    | 0 / 152 (0.00%) |  |  |
| occurrences (all)                              | 0               |  |  |
| Partial seizures with secondary generalisation |                 |  |  |
| subjects affected / exposed                    | 0 / 152 (0.00%) |  |  |
| occurrences (all)                              | 0               |  |  |
| Poor quality sleep                             |                 |  |  |
| subjects affected / exposed                    | 0 / 152 (0.00%) |  |  |
| occurrences (all)                              | 0               |  |  |
| Postictal headache                             |                 |  |  |
| subjects affected / exposed                    | 0 / 152 (0.00%) |  |  |
| occurrences (all)                              | 0               |  |  |
| Postictal state                                |                 |  |  |
| subjects affected / exposed                    | 0 / 152 (0.00%) |  |  |
| occurrences (all)                              | 0               |  |  |
| Psychomotor hyperactivity                      |                 |  |  |
| subjects affected / exposed                    | 0 / 152 (0.00%) |  |  |
| occurrences (all)                              | 0               |  |  |
| Somnolence                                     |                 |  |  |
| subjects affected / exposed                    | 3 / 152 (1.97%) |  |  |
| occurrences (all)                              | 3               |  |  |
| Speech disorder                                |                 |  |  |
| subjects affected / exposed                    | 0 / 152 (0.00%) |  |  |
| occurrences (all)                              | 0               |  |  |

|   |                      |  |  |
|---|----------------------|--|--|
| Status epilepticus<br>subjects affected / exposed<br>occurrences (all)      | 0 / 152 (0.00%)<br>0 |  |  |
| Syncope<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 152 (0.00%)<br>0 |  |  |
| Tremor<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 152 (0.00%)<br>0 |  |  |
| Unresponsive to stimuli<br>subjects affected / exposed<br>occurrences (all) | 0 / 152 (0.00%)<br>0 |  |  |
| Blood and lymphatic system disorders  |                      |  |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 152 (0.66%)<br>1 |  |  |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)              | 0 / 152 (0.00%)<br>0 |  |  |
| Lymphadenopathy<br>subjects affected / exposed<br>occurrences (all)         | 0 / 152 (0.00%)<br>0 |  |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)             | 0 / 152 (0.00%)<br>0 |  |  |
| Pancytopenia<br>subjects affected / exposed<br>occurrences (all)            | 2 / 152 (1.32%)<br>2 |  |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)        | 1 / 152 (0.66%)<br>2 |  |  |
| Ear and labyrinth disorders   |                      |  |  |
| Ear pain<br>subjects affected / exposed<br>occurrences (all)                | 0 / 152 (0.00%)<br>0 |  |  |
| Tinnitus  |                      |  |  |

|   |                      |  |  |
|---|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                                  | 0 / 152 (0.00%)<br>0 |  |  |
| Tympanic membrane perforation<br>subjects affected / exposed<br>occurrences (all) | 0 / 152 (0.00%)<br>0 |  |  |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 152 (0.00%)<br>0 |  |  |
| Eye disorders   |                      |  |  |
| Abnormal sensation in eye<br>subjects affected / exposed<br>occurrences (all)     | 0 / 152 (0.00%)<br>0 |  |  |
| Astigmatism<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 152 (0.00%)<br>0 |  |  |
| Conjunctival haemorrhage<br>subjects affected / exposed<br>occurrences (all)      | 0 / 152 (0.00%)<br>0 |  |  |
| Diplopia<br>subjects affected / exposed<br>occurrences (all)                      | 2 / 152 (1.32%)<br>2 |  |  |
| Eye pain<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 152 (0.00%)<br>0 |  |  |
| Eye swelling<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 152 (0.00%)<br>0 |  |  |
| Lacrimation increased<br>subjects affected / exposed<br>occurrences (all)         | 0 / 152 (0.00%)<br>0 |  |  |
| Optic atrophy<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 152 (0.00%)<br>0 |  |  |
| Vision blurred<br>subjects affected / exposed<br>occurrences (all)                | 1 / 152 (0.66%)<br>1 |  |  |

|  |                       |  |  |
|--|-----------------------|--|--|
| Visual impairment<br>subjects affected / exposed<br>occurrences (all)    | 0 / 152 (0.00%)<br>0  |  |  |
| <b>Gastrointestinal disorders</b>  |                       |  |  |
| Abdominal distension<br>subjects affected / exposed<br>occurrences (all) | 0 / 152 (0.00%)<br>0  |  |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | 2 / 152 (1.32%)<br>6  |  |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | 1 / 152 (0.66%)<br>1  |  |  |
| Aphthous stomatitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 152 (0.00%)<br>0  |  |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)         | 1 / 152 (0.66%)<br>1  |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 9 / 152 (5.92%)<br>11 |  |  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)            | 0 / 152 (0.00%)<br>0  |  |  |
| Dysphagia<br>subjects affected / exposed<br>occurrences (all)            | 1 / 152 (0.66%)<br>1  |  |  |
| Enteritis<br>subjects affected / exposed<br>occurrences (all)            | 1 / 152 (0.66%)<br>1  |  |  |
| Enterocolitis<br>subjects affected / exposed<br>occurrences (all)        | 5 / 152 (3.29%)<br>6  |  |  |
| Flatulence   |                       |  |  |

|                                  |                 |  |  |
|----------------------------------|-----------------|--|--|
| subjects affected / exposed      | 0 / 152 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Food poisoning                   |                 |  |  |
| subjects affected / exposed      | 0 / 152 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Frequent bowel movements         |                 |  |  |
| subjects affected / exposed      | 1 / 152 (0.66%) |  |  |
| occurrences (all)                | 1               |  |  |
| Gastritis                        |                 |  |  |
| subjects affected / exposed      | 0 / 152 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Gastroduodenitis                 |                 |  |  |
| subjects affected / exposed      | 0 / 152 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Gastrooesophageal reflux disease |                 |  |  |
| subjects affected / exposed      | 0 / 152 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Gingival bleeding                |                 |  |  |
| subjects affected / exposed      | 1 / 152 (0.66%) |  |  |
| occurrences (all)                | 2               |  |  |
| Gingivitis                       |                 |  |  |
| subjects affected / exposed      | 0 / 152 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Irritable bowel syndrome         |                 |  |  |
| subjects affected / exposed      | 0 / 152 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Lip dry                          |                 |  |  |
| subjects affected / exposed      | 0 / 152 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Mouth ulceration                 |                 |  |  |
| subjects affected / exposed      | 0 / 152 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Nausea                           |                 |  |  |
| subjects affected / exposed      | 1 / 152 (0.66%) |  |  |
| occurrences (all)                | 1               |  |  |
| Odynophagia                      |                 |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Oesophagitis                |                 |  |  |
| subjects affected / exposed | 1 / 152 (0.66%) |  |  |
| occurrences (all)           | 1               |  |  |
| Oral pain                   |                 |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Pancreatic disorder         |                 |  |  |
| subjects affected / exposed | 1 / 152 (0.66%) |  |  |
| occurrences (all)           | 1               |  |  |
| Periodontitis               |                 |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Peritonitis                 |                 |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Rectal fissure              |                 |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Salivary hypersecretion     |                 |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Stomatitis                  |                 |  |  |
| subjects affected / exposed | 1 / 152 (0.66%) |  |  |
| occurrences (all)           | 1               |  |  |
| Tooth disorder              |                 |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Toothache                   |                 |  |  |
| subjects affected / exposed | 1 / 152 (0.66%) |  |  |
| occurrences (all)           | 1               |  |  |
| Vomiting                    |                 |  |  |
| subjects affected / exposed | 9 / 152 (5.92%) |  |  |
| occurrences (all)           | 13              |  |  |
| Hepatobiliary disorders     |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Biliary dyskinesia                            |                 |  |  |
| subjects affected / exposed                   | 0 / 152 (0.00%) |  |  |
| occurrences (all)                             | 0               |  |  |
| Hepatic cyst                                  |                 |  |  |
| subjects affected / exposed                   | 1 / 152 (0.66%) |  |  |
| occurrences (all)                             | 1               |  |  |
| Hepatic steatosis                             |                 |  |  |
| subjects affected / exposed                   | 0 / 152 (0.00%) |  |  |
| occurrences (all)                             | 0               |  |  |
| <b>Skin and subcutaneous tissue disorders</b> |                 |  |  |
| Acne  |                 |  |  |
| subjects affected / exposed                   | 0 / 152 (0.00%) |  |  |
| occurrences (all)                             | 0               |  |  |
| Alopecia                                      |                 |  |  |
| subjects affected / exposed                   | 0 / 152 (0.00%) |  |  |
| occurrences (all)                             | 0               |  |  |
| Dermatitis                                    |                 |  |  |
| subjects affected / exposed                   | 0 / 152 (0.00%) |  |  |
| occurrences (all)                             | 0               |  |  |
| Dermatitis acneiform                          |                 |  |  |
| subjects affected / exposed                   | 0 / 152 (0.00%) |  |  |
| occurrences (all)                             | 0               |  |  |
| Dermatitis allergic                           |                 |  |  |
| subjects affected / exposed                   | 1 / 152 (0.66%) |  |  |
| occurrences (all)                             | 1               |  |  |
| Dermatitis atopic                             |                 |  |  |
| subjects affected / exposed                   | 1 / 152 (0.66%) |  |  |
| occurrences (all)                             | 1               |  |  |
| Dermatitis contact                            |                 |  |  |
| subjects affected / exposed                   | 0 / 152 (0.00%) |  |  |
| occurrences (all)                             | 0               |  |  |
| Dermatitis diaper                             |                 |  |  |
| subjects affected / exposed                   | 0 / 152 (0.00%) |  |  |
| occurrences (all)                             | 0               |  |  |
| Dry skin                                      |                 |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Heat rash                   |                 |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Ingrowing nail              |                 |  |  |
| subjects affected / exposed | 1 / 152 (0.66%) |  |  |
| occurrences (all)           | 1               |  |  |
| Onychomadesis               |                 |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Papule                      |                 |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Pityriasis rosea            |                 |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Pruritus                    |                 |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Rash                        |                 |  |  |
| subjects affected / exposed | 1 / 152 (0.66%) |  |  |
| occurrences (all)           | 1               |  |  |
| Rash erythematous           |                 |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Rash pruritic               |                 |  |  |
| subjects affected / exposed | 1 / 152 (0.66%) |  |  |
| occurrences (all)           | 1               |  |  |
| Skin exfoliation            |                 |  |  |
| subjects affected / exposed | 1 / 152 (0.66%) |  |  |
| occurrences (all)           | 1               |  |  |
| Solar dermatitis            |                 |  |  |
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Urticaria                   |                 |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 152 (0.00%)<br>0 |  |  |
| <b>Renal and urinary disorders</b>               |                      |  |  |
| <b>Dysuria</b>                                   |                      |  |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 152 (0.66%)<br>1 |  |  |
| <b>Enuresis</b>                                  |                      |  |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 152 (0.66%)<br>1 |  |  |
| <b>Haematuria</b>                                |                      |  |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 152 (0.00%)<br>0 |  |  |
| <b>Incontinence</b>                              |                      |  |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 152 (0.66%)<br>2 |  |  |
| <b>Leukocyturia</b>                              |                      |  |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 152 (0.66%)<br>1 |  |  |
| <b>Nephropathy</b>                               |                      |  |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 152 (0.00%)<br>0 |  |  |
| <b>Nocturia</b>                                  |                      |  |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 152 (0.00%)<br>0 |  |  |
| <b>Renal failure acute</b>                       |                      |  |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 152 (0.66%)<br>1 |  |  |
| <b>Urinary retention</b>                         |                      |  |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 152 (0.00%)<br>0 |  |  |
| <b>Endocrine disorders</b>                       |                      |  |  |
| <b>Goitre</b>                                    |                      |  |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 152 (0.66%)<br>1 |  |  |
| <b>Hypothalamo-pituitary disorder</b>            |                      |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                       | 1 / 152 (0.66%)<br>1 |  |  |
| Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)     | 3 / 152 (1.97%)<br>3 |  |  |
| Precocious puberty<br>subjects affected / exposed<br>occurrences (all) | 0 / 152 (0.00%)<br>0 |  |  |
| Musculoskeletal and connective tissue disorders                        |                      |  |  |
| Ankle deformity<br>subjects affected / exposed<br>occurrences (all)    | 1 / 152 (0.66%)<br>1 |  |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)         | 2 / 152 (1.32%)<br>2 |  |  |
| Arthritis reactive<br>subjects affected / exposed<br>occurrences (all) | 0 / 152 (0.00%)<br>0 |  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)          | 0 / 152 (0.00%)<br>0 |  |  |
| Chest wall mass<br>subjects affected / exposed<br>occurrences (all)    | 0 / 152 (0.00%)<br>0 |  |  |
| Elbow deformity<br>subjects affected / exposed<br>occurrences (all)    | 0 / 152 (0.00%)<br>0 |  |  |
| Foot deformity<br>subjects affected / exposed<br>occurrences (all)     | 2 / 152 (1.32%)<br>2 |  |  |
| Groin pain<br>subjects affected / exposed<br>occurrences (all)         | 0 / 152 (0.00%)<br>0 |  |  |
| Haemarthrosis  |                      |  |  |

|   |                        |  |  |
|---|------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                      | 1 / 152 (0.66%)<br>1   |  |  |
| Joint swelling<br>subjects affected / exposed<br>occurrences (all)    | 0 / 152 (0.00%)<br>0   |  |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)           | 1 / 152 (0.66%)<br>1   |  |  |
| Neck pain<br>subjects affected / exposed<br>occurrences (all)         | 0 / 152 (0.00%)<br>0   |  |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all) | 2 / 152 (1.32%)<br>2   |  |  |
| Rhabdomyolysis<br>subjects affected / exposed<br>occurrences (all)    | 1 / 152 (0.66%)<br>1   |  |  |
| <b>Infections and infestations</b>                                    |                        |  |  |
| Abscess limb<br>subjects affected / exposed<br>occurrences (all)      | 0 / 152 (0.00%)<br>0   |  |  |
| Acute sinusitis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 152 (0.66%)<br>3   |  |  |
| Acute tonsillitis<br>subjects affected / exposed<br>occurrences (all) | 2 / 152 (1.32%)<br>2   |  |  |
| Appendicitis<br>subjects affected / exposed<br>occurrences (all)      | 0 / 152 (0.00%)<br>0   |  |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)        | 11 / 152 (7.24%)<br>13 |  |  |
| Bronchopneumonia<br>subjects affected / exposed<br>occurrences (all)  | 2 / 152 (1.32%)<br>2   |  |  |

|                                  |                 |  |  |
|----------------------------------|-----------------|--|--|
| Bullous impetigo                 |                 |  |  |
| subjects affected / exposed      | 0 / 152 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Conjunctivitis bacterial         |                 |  |  |
| subjects affected / exposed      | 0 / 152 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Cystitis                         |                 |  |  |
| subjects affected / exposed      | 1 / 152 (0.66%) |  |  |
| occurrences (all)                | 1               |  |  |
| Ear infection                    |                 |  |  |
| subjects affected / exposed      | 0 / 152 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Febrile infection                |                 |  |  |
| subjects affected / exposed      | 0 / 152 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Fungal skin infection            |                 |  |  |
| subjects affected / exposed      | 0 / 152 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Gastroenteritis                  |                 |  |  |
| subjects affected / exposed      | 7 / 152 (4.61%) |  |  |
| occurrences (all)                | 9               |  |  |
| Gastroenteritis viral            |                 |  |  |
| subjects affected / exposed      | 2 / 152 (1.32%) |  |  |
| occurrences (all)                | 3               |  |  |
| Gastrointestinal viral infection |                 |  |  |
| subjects affected / exposed      | 0 / 152 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Helicobacter infection           |                 |  |  |
| subjects affected / exposed      | 0 / 152 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Herpes simplex                   |                 |  |  |
| subjects affected / exposed      | 0 / 152 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Hordeolum                        |                 |  |  |
| subjects affected / exposed      | 1 / 152 (0.66%) |  |  |
| occurrences (all)                | 1               |  |  |

|                                   |                  |  |  |
|-----------------------------------|------------------|--|--|
| Impetigo                          |                  |  |  |
| subjects affected / exposed       | 0 / 152 (0.00%)  |  |  |
| occurrences (all)                 | 0                |  |  |
| Infected bites                    |                  |  |  |
| subjects affected / exposed       | 0 / 152 (0.00%)  |  |  |
| occurrences (all)                 | 0                |  |  |
| Infection                         |                  |  |  |
| subjects affected / exposed       | 0 / 152 (0.00%)  |  |  |
| occurrences (all)                 | 0                |  |  |
| Influenza                         |                  |  |  |
| subjects affected / exposed       | 5 / 152 (3.29%)  |  |  |
| occurrences (all)                 | 7                |  |  |
| Laryngitis                        |                  |  |  |
| subjects affected / exposed       | 1 / 152 (0.66%)  |  |  |
| occurrences (all)                 | 2                |  |  |
| Lower respiratory tract infection |                  |  |  |
| subjects affected / exposed       | 0 / 152 (0.00%)  |  |  |
| occurrences (all)                 | 0                |  |  |
| Mastitis                          |                  |  |  |
| subjects affected / exposed       | 1 / 152 (0.66%)  |  |  |
| occurrences (all)                 | 1                |  |  |
| Nasopharyngitis                   |                  |  |  |
| subjects affected / exposed       | 15 / 152 (9.87%) |  |  |
| occurrences (all)                 | 24               |  |  |
| Onychomycosis                     |                  |  |  |
| subjects affected / exposed       | 0 / 152 (0.00%)  |  |  |
| occurrences (all)                 | 0                |  |  |
| Oral herpes                       |                  |  |  |
| subjects affected / exposed       | 0 / 152 (0.00%)  |  |  |
| occurrences (all)                 | 0                |  |  |
| Otitis externa                    |                  |  |  |
| subjects affected / exposed       | 0 / 152 (0.00%)  |  |  |
| occurrences (all)                 | 0                |  |  |
| Otitis media                      |                  |  |  |
| subjects affected / exposed       | 2 / 152 (1.32%)  |  |  |
| occurrences (all)                 | 2                |  |  |

|                                   |                 |  |  |
|-----------------------------------|-----------------|--|--|
| Otitis media acute                |                 |  |  |
| subjects affected / exposed       | 1 / 152 (0.66%) |  |  |
| occurrences (all)                 | 1               |  |  |
| Parasitic gastroenteritis         |                 |  |  |
| subjects affected / exposed       | 0 / 152 (0.00%) |  |  |
| occurrences (all)                 | 0               |  |  |
| Paronychia                        |                 |  |  |
| subjects affected / exposed       | 1 / 152 (0.66%) |  |  |
| occurrences (all)                 | 1               |  |  |
| Pharyngitis                       |                 |  |  |
| subjects affected / exposed       | 9 / 152 (5.92%) |  |  |
| occurrences (all)                 | 18              |  |  |
| Pharyngotonsillitis               |                 |  |  |
| subjects affected / exposed       | 5 / 152 (3.29%) |  |  |
| occurrences (all)                 | 6               |  |  |
| Pneumonia                         |                 |  |  |
| subjects affected / exposed       | 3 / 152 (1.97%) |  |  |
| occurrences (all)                 | 3               |  |  |
| Pulmonary tuberculosis            |                 |  |  |
| subjects affected / exposed       | 0 / 152 (0.00%) |  |  |
| occurrences (all)                 | 0               |  |  |
| Pulpitis dental                   |                 |  |  |
| subjects affected / exposed       | 1 / 152 (0.66%) |  |  |
| occurrences (all)                 | 1               |  |  |
| Respiratory tract infection       |                 |  |  |
| subjects affected / exposed       | 6 / 152 (3.95%) |  |  |
| occurrences (all)                 | 14              |  |  |
| Respiratory tract infection viral |                 |  |  |
| subjects affected / exposed       | 0 / 152 (0.00%) |  |  |
| occurrences (all)                 | 0               |  |  |
| Rhinitis                          |                 |  |  |
| subjects affected / exposed       | 9 / 152 (5.92%) |  |  |
| occurrences (all)                 | 20              |  |  |
| Sinusitis                         |                 |  |  |
| subjects affected / exposed       | 2 / 152 (1.32%) |  |  |
| occurrences (all)                 | 2               |  |  |

|                                   |                  |  |  |
|-----------------------------------|------------------|--|--|
| Subcutaneous abscess              |                  |  |  |
| subjects affected / exposed       | 1 / 152 (0.66%)  |  |  |
| occurrences (all)                 | 1                |  |  |
| Tinea infection                   |                  |  |  |
| subjects affected / exposed       | 0 / 152 (0.00%)  |  |  |
| occurrences (all)                 | 0                |  |  |
| Tonsillitis                       |                  |  |  |
| subjects affected / exposed       | 5 / 152 (3.29%)  |  |  |
| occurrences (all)                 | 7                |  |  |
| Tracheitis                        |                  |  |  |
| subjects affected / exposed       | 1 / 152 (0.66%)  |  |  |
| occurrences (all)                 | 2                |  |  |
| Tracheobronchitis                 |                  |  |  |
| subjects affected / exposed       | 1 / 152 (0.66%)  |  |  |
| occurrences (all)                 | 1                |  |  |
| Upper respiratory tract infection |                  |  |  |
| subjects affected / exposed       | 12 / 152 (7.89%) |  |  |
| occurrences (all)                 | 17               |  |  |
| Urinary tract infection           |                  |  |  |
| subjects affected / exposed       | 1 / 152 (0.66%)  |  |  |
| occurrences (all)                 | 1                |  |  |
| Urinary tract infection bacterial |                  |  |  |
| subjects affected / exposed       | 0 / 152 (0.00%)  |  |  |
| occurrences (all)                 | 0                |  |  |
| Varicella                         |                  |  |  |
| subjects affected / exposed       | 2 / 152 (1.32%)  |  |  |
| occurrences (all)                 | 2                |  |  |
| Viral infection                   |                  |  |  |
| subjects affected / exposed       | 9 / 152 (5.92%)  |  |  |
| occurrences (all)                 | 11               |  |  |
| Viral pharyngitis                 |                  |  |  |
| subjects affected / exposed       | 1 / 152 (0.66%)  |  |  |
| occurrences (all)                 | 1                |  |  |
| Viral rash                        |                  |  |  |
| subjects affected / exposed       | 0 / 152 (0.00%)  |  |  |
| occurrences (all)                 | 0                |  |  |

|   |                      |  |  |
|---|----------------------|--|--|
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 152 (0.66%)<br>1 |  |  |
| Vulvitis<br>subjects affected / exposed<br>occurrences (all)                                | 1 / 152 (0.66%)<br>1 |  |  |
| <b>Metabolism and nutrition disorders</b>   |                      |  |  |
| Appetite disorder<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 152 (0.00%)<br>0 |  |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                      | 2 / 152 (1.32%)<br>2 |  |  |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 152 (0.00%)<br>0 |  |  |
| Feeding disorder<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 152 (0.00%)<br>0 |  |  |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 152 (0.66%)<br>1 |  |  |
| Hyperphagia<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 152 (0.00%)<br>0 |  |  |
| Increased appetite<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 152 (0.00%)<br>0 |  |  |
| Iron deficiency<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 152 (0.00%)<br>0 |  |  |
| Obesity<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 152 (0.00%)<br>0 |  |  |
| Weight gain poor  |                      |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 152 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 20 December 2007  | Global Amendment#1<br>The reason for this study global protocol amendment is to harmonized the requests from different Ethics Committees and/or Regulatory Authorities                                    |
| 29 April 2009     | Global Amendment#2<br>The reason is to define a study extension (Part III) in order to allow patients who participated in study SCO/BIA-2093-305 to continue receiving the study medication               |
| 17 May 2010       | Global Amendment#3<br>The reason is to define a study extension (Part IV) in order to allow patients who participated in study SCO/BIA-2093-305 to continue receiving the study medication                |
| 07 June 2010      | Global Amendment#4<br>The reason is the recall of the oral suspension formulation of the investigational medicinal product (50 mg/mL) used in the age group of 2-6 years children for Part I and Part II. |
| 16 September 2010 | Global Amendment#4<br>The reason is the recall of the oral suspension formulation of the investigational medicinal product (50 mg/mL) used in the age group of 2-6 years children for Part I and Part II. |
| 12 May 2011       | Global Amendment#3<br>The reason is to define a study extension (Part V) in order to allow patients who participated in study SCO/BIA-2093-305 to continue receiving the study medication                 |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported