



## Clinical trial results:

### A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease

#### Summary

|                          |                            |
|--------------------------|----------------------------|
| EudraCT number           | 2015-000967-15             |
| Trial protocol           | DE SE NL ES BE FR PL FI IT |
| Global end of trial date | 05 August 2019             |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v2 (current)     |
| This version publication date  | 06 October 2021  |
| First version publication date | 20 November 2020 |
| Version creation reason        |                  |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 221AD302 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02484547 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Biogen   |
| Sponsor organisation address | 250 Binney Street, Cambridge, United States, 02142               |
| Public contact               | Biogen Study Medical director, Biogen, clinicaltrials@biogen.com |
| Scientific contact           | Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                |
|--|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 05 August 2019 |
| Is this the analysis of the primary completion data? | No             |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 05 August 2019 |
| Was the trial ended prematurely?                     | Yes            |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the efficacy of monthly doses of aducanumab in slowing cognitive and functional impairment as measured by changes in the Clinical Dementia Rating Sum of Boxes (CDR-SB) score as compared with placebo in participants with early Alzheimer's disease.

Protection of trial subjects:

Written informed consent was obtained from each subject or subject's legally authorized representative (e.g., legal guardian), as applicable, prior to evaluations performed for eligibility. Subjects or the subject's legally authorized representative were given adequate time to review the information in the informed consent/assent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study.

Background therapy: -

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 15 September 2015 |
| Long term follow-up planned                               | Yes               |
| Long term follow-up rationale                             | Safety            |
| Long term follow-up duration                              | 4 Months          |
| Independent data monitoring committee (IDMC) involvement? | Yes               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 652 |
| Country: Number of subjects enrolled | Poland: 193        |
| Country: Number of subjects enrolled | Germany: 122       |
| Country: Number of subjects enrolled | Japan: 121         |
| Country: Number of subjects enrolled | Canada: 96         |
| Country: Number of subjects enrolled | Italy: 82          |
| Country: Number of subjects enrolled | France: 79         |
| Country: Number of subjects enrolled | Spain: 78          |
| Country: Number of subjects enrolled | Switzerland: 52    |
| Country: Number of subjects enrolled | Belgium: 49        |
| Country: Number of subjects enrolled | Netherlands: 49    |
| Country: Number of subjects enrolled | Sweden: 37         |
| Country: Number of subjects enrolled | Finland: 33        |
| Worldwide total number of subjects   | 1643               |
| EEA total number of subjects         | 722                |

Notes:

| <b>Subjects enrolled per age group</b>    |      |
|---|------|
| In utero                                  | 0    |
| Preterm newborn - gestational age < 37 wk | 0    |
| Newborns (0-27 days)                      | 0    |
| Infants and toddlers (28 days-23 months)  | 0    |
| Children (2-11 years)                     | 0    |
| Adolescents (12-17 years)                 | 0    |
| Adults (18-64 years)                      | 324  |
| From 65 to 84 years                       | 1303 |
| 85 years and over                         | 16   |

## Subject disposition

### Recruitment

Recruitment details:

Subjects were enrolled at 181 investigative sites in the United States, Belgium, Canada, Finland, France, Germany, Italy, Japan, Netherlands, Poland, Spain, Sweden, and Switzerland from 15 September 2015 to 13 July 2018.

### Pre-assignment

Screening details:

A total of 1643 subjects with Alzheimer's disease were enrolled and randomised in the study. Of these, 1638 subjects received the study drug in placebo-controlled (PC) period. After completing PC period, 771 subjects entered and dosed in long-term extension (LTE) period and no subjects completed the study due to early termination of the study.

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | Placebo-Controlled Period                            |
| Is this the baseline period? | Yes  |
| Allocation method            | Randomised - controlled                              |
| Blinding used                | Double blind   |
| Roles blinded                | Subject, Investigator, Carer, Data analyst, Assessor |

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | Placebo (PC Period) |
|------------------|---------------------|

Arm description:

Subjects received a maximum of 20 infusions of BIIB037-matching placebo intravenously (IV) in PC period, administered approximately once every 4 weeks for up to approximately 1.5 years.

|  |                                       |
|--|---------------------------------------|
| Arm type                               | Placebo                               |
| Investigational medicinal product name | Placebo                               |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Intravenous infusion, once every 4 weeks.

|                  |                              |
|------------------|------------------------------|
| <b>Arm title</b> | BIIB037 Low Dose (PC Period) |
|------------------|------------------------------|

Arm description:

Subjects received a maximum of 20 infusions of BIIB037 low dose IV in PC period, administered approximately once every 4 weeks for up to approximately 1.5 years.

|  |                                       |
|--|---------------------------------------|
| Arm type                               | Experimental                          |
| Investigational medicinal product name | BIIB037                               |
| Investigational medicinal product code |                                       |
| Other name                             | Aducanumab                            |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Intravenous infusion, once every 4 weeks.

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | BIIB037 High Dose (PC Period) |
|------------------|-------------------------------|

Arm description:

Subjects received a maximum of 20 infusions of BIIB037 high dose IV in PC period, administered approximately once every 4 weeks for up to approximately 1.5 years.

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

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | BIIB037                               |
| Investigational medicinal product code |                                       |
| Other name                             | Aducanumab                            |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Intravenous infusion, once every 4 weeks.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Placebo (PC Period) | BIIB037 Low Dose (PC Period) | BIIB037 High Dose (PC Period) |
|---|---------------------|------------------------------|-------------------------------|
| Started   | 548                 | 543                          | 547                           |
| Completed   | 288                 | 291                          | 295                           |
| Not completed                                       | 260                 | 252                          | 252                           |
| Relocation  | 1                   | 1                            | 1                             |
| Adverse Event                                       | 10                  | 13                           | 20                            |
| Death   | 5                   | -                            | 6                             |
| Withdrawal by Parent/Guardian                       | 4                   | 1                            | 1                             |
| Investigator Decision                               | 2                   | 2                            | 5                             |
| Lost to follow-up                                   | 3                   | 1                            | 3                             |
| Study Visit Burden                                  | 2                   | 8                            | 5                             |
| Disease Progression                                 | 2                   | -                            | 1                             |
| Reason not Specified                                | 216                 | 194                          | 183                           |
| Change of Treatment                                 | -                   | -                            | 1                             |
| Consent Withdrawn                                   | 15                  | 32                           | 26                            |

Notes:

[1] - 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: The number of subjects reported in the baseline period is for intent to treat population (548 subjects in placebo arm, 543 subjects in BIIB037 Low Dose arm, 547 subjects in BIIB037 High Dose arm).

## Period 2

|                              |  |
|------------------------------|--|
| Period 2 title               | Long-Term Extension Period                           |
| Is this the baseline period? | No   |
| Allocation method            | Randomised - controlled                              |
| Blinding used                | Double blind   |
| Roles blinded                | Subject, Investigator, Carer, Data analyst, Assessor |

## Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|   |   |
|---|---|
| <b>Arm title</b>  | BIIB037 Late Start: Low Dose (LTE Period)   |
| Arm description:<br>Following PC period, subjects randomised to placebo received BIIB037 low dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period.                    |   |
| Arm type  | Experimental                                |
| Investigational medicinal product name  | BIIB037                                     |
| Investigational medicinal product code  |   |
| Other name  | Aducanumab                                  |
| Pharmaceutical forms  | Concentrate for solution for infusion       |
| Routes of administration  | Intravenous use                             |
| Dosage and administration details:<br>Intravenous infusion, once every 4 weeks.   |   |
| <b>Arm title</b>  | BIIB037 Late Start: High Dose (LTE Period)  |
| Arm description:<br>Following PC period, subjects randomised to placebo received BIIB037 high dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period.                   |   |
| Arm type  | Experimental                                |
| Investigational medicinal product name  | BIIB037                                     |
| Investigational medicinal product code  |   |
| Other name  | Aducanumab                                  |
| Pharmaceutical forms  | Concentrate for solution for infusion       |
| Routes of administration  | Intravenous use                             |
| Dosage and administration details:<br>Intravenous infusion, once every 4 weeks.   |   |
| <b>Arm title</b>  | BIIB037 Early Start: Low Dose (LTE Period)  |
| Arm description:<br>Following PC period, subjects randomised to low dose BIIB037 continued to receive the same dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period.  |   |
| Arm type  | Experimental                                |
| Investigational medicinal product name  | BIIB037                                     |
| Investigational medicinal product code  |   |
| Other name  | Aducanumab                                  |
| Pharmaceutical forms  | Concentrate for solution for infusion       |
| Routes of administration  | Intravenous use                             |
| Dosage and administration details:<br>Intravenous infusion, once every 4 weeks.   |   |
| <b>Arm title</b>  | BIIB037 Early Start: High Dose (LTE Period) |
| Arm description:<br>Following PC period, subjects randomised to high dose BIIB037 continued to receive the same dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period. |   |
| Arm type  | Experimental                                |
| Investigational medicinal product name  | BIIB037                                     |
| Investigational medicinal product code  |   |
| Other name  | Aducanumab                                  |
| Pharmaceutical forms  | Concentrate for solution for infusion       |
| Routes of administration  | Intravenous use                             |
| Dosage and administration details:<br>Intravenous infusion, once every 4 weeks.   |   |

| <b>Number of subjects in period 2<sup>[2]</sup></b> | <b>BIIB037 Late Start: Low Dose (LTE Period)</b> | <b>BIIB037 Late Start: High Dose (LTE Period)</b> | <b>BIIB037 Early Start: Low Dose (LTE Period)</b> |
|---|--|---|---|
| Started   | 131  | 132   | 251   |
| Completed   | 0  | 0   | 0   |
| Not completed                                       | 131  | 132   | 251   |
| Relocation  | 1  | 1   | -   |
| Loss of Capacity                                    | -  | 1   | -   |
| Adverse Event                                       | -  | 1   | 3   |
| Death   | -  | -   | 3   |
| Withdrawal by Parent/Guardian                       | -  | 1   | 3   |
| Investigator Decision                               | 2  | 1   | -   |
| Lost to follow-up                                   | 1  | 1   | 2   |
| Study Visit Burden                                  | 2  | -   | -   |
| Reason not Specified                                | 119  | 117   | 223   |
| Disease Progression                                 | -  | 2   | 4   |
| Change of Treatment                                 | -  | -   | -   |
| Consent Withdrawn                                   | 6  | 7   | 13  |

| <b>Number of subjects in period 2<sup>[2]</sup></b> | <b>BIIB037 Early Start: High Dose (LTE Period)</b> |
|---|--|
| Started   | 257  |
| Completed   | 0  |
| Not completed                                       | 257  |
| Relocation  | -  |
| Loss of Capacity                                    | -  |
| Adverse Event                                       | 2  |
| Death   | -  |
| Withdrawal by Parent/Guardian                       | 2  |
| Investigator Decision                               | 1  |
| Lost to follow-up                                   | -  |
| Study Visit Burden                                  | 3  |
| Reason not Specified                                | 231  |
| Disease Progression                                 | -  |
| Change of Treatment                                 | 1  |
| Consent Withdrawn                                   | 17   |

Notes:

[2] - 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: 874 subjects completed the PC period, out of which only 771 subjects entered in LTE period. 103 subjects from PC period did not enter LTE period.

## Baseline characteristics

### Reporting groups

|   |                               |
|---|-------------------------------|
| Reporting group title   | Placebo (PC Period)           |
| Reporting group description:  |                               |
| Subjects received a maximum of 20 infusions of BIIB037-matching placebo intravenously (IV) in PC period, administered approximately once every 4 weeks for up to approximately 1.5 years. |                               |
| Reporting group title   | BIIB037 Low Dose (PC Period)  |
| Reporting group description:  |                               |
| Subjects received a maximum of 20 infusions of BIIB037 low dose IV in PC period, administered approximately once every 4 weeks for up to approximately 1.5 years.                         |                               |
| Reporting group title   | BIIB037 High Dose (PC Period) |
| Reporting group description:  |                               |
| Subjects received a maximum of 20 infusions of BIIB037 high dose IV in PC period, administered approximately once every 4 weeks for up to approximately 1.5 years.                        |                               |

| Reporting group values | Placebo (PC Period) | BIIB037 Low Dose (PC Period) | BIIB037 High Dose (PC Period) |
|------------------------|---------------------|------------------------------|-------------------------------|
| Number of subjects     | 548                 | 543                          | 547                           |
| Age categorical        |                     |                              |                               |
| Units: Subjects        |                     |                              |                               |

|   |        |        |        |
|---|--------|--------|--------|
| Age Continuous                                  |        |        |        |
| Units: years                                    |        |        |        |
| arithmetic mean                                 | 70.8   | 70.6   | 70.6   |
| standard deviation                              | ± 7.40 | ± 7.45 | ± 7.47 |
| Sex: Female, Male                               |        |        |        |
| Units: subjects                                 |        |        |        |
| Female  | 290    | 269    | 284    |
| Male  | 258    | 274    | 263    |
| Race  |        |        |        |
| Units: Subjects                                 |        |        |        |
| American Indian or Alaska Native                | 1      | 0      | 0      |
| Asian   | 47     | 39     | 42     |
| Black or African American                       | 1      | 6      | 4      |
| White   | 431    | 432    | 422    |
| Not Reported due to Confidentiality Regulations | 67     | 65     | 75     |
| Other   | 1      | 1      | 3      |
| Unknown   | 0      | 0      | 1      |
| Ethnicity                                       |        |        |        |
| Units: Subjects                                 |        |        |        |
| Hispanic or Latino                              | 22     | 22     | 23     |
| Not Hispanic or Latino                          | 470    | 470    | 461    |
| Not reported due to confidentiality regulations | 56     | 51     | 62     |
| Unknown   | 0      | 0      | 1      |

| Reporting group values | Total |  |  |
|------------------------|-------|--|--|
| Number of subjects     | 1638  |  |  |



|   |      |  |  |
|---|------|--|--|
| Age categorical<br>Units: Subjects                                      |      |  |  |
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -    |  |  |
| Sex: Female, Male<br>Units: subjects                                    |      |  |  |
| Female  | 843  |  |  |
| Male  | 795  |  |  |
| Race<br>Units: Subjects   |      |  |  |
| American Indian or Alaska Native  | 1    |  |  |
| Asian   | 128  |  |  |
| Black or African American   | 11   |  |  |
| White   | 1285 |  |  |
| Not Reported due to Confidentiality Regulations                         | 207  |  |  |
| Other   | 5    |  |  |
| Unknown   | 1    |  |  |
| Ethnicity<br>Units: Subjects  |      |  |  |
| Hispanic or Latino  | 67   |  |  |
| Not Hispanic or Latino  | 1401 |  |  |
| Not reported due to confidentiality regulations                         | 169  |  |  |
| Unknown   | 1    |  |  |

## End points

### End points reporting groups

|   |   |
|---|---|
| Reporting group title   | Placebo (PC Period)                         |
| Reporting group description:<br>Subjects received a maximum of 20 infusions of BIIB037-matching placebo intravenously (IV) in PC period, administered approximately once every 4 weeks for up to approximately 1.5 years. |   |
| Reporting group title   | BIIB037 Low Dose (PC Period)                |
| Reporting group description:<br>Subjects received a maximum of 20 infusions of BIIB037 low dose IV in PC period, administered approximately once every 4 weeks for up to approximately 1.5 years.                         |   |
| Reporting group title   | BIIB037 High Dose (PC Period)               |
| Reporting group description:<br>Subjects received a maximum of 20 infusions of BIIB037 high dose IV in PC period, administered approximately once every 4 weeks for up to approximately 1.5 years.                        |   |
| Reporting group title   | BIIB037 Late Start: Low Dose (LTE Period)   |
| Reporting group description:<br>Following PC period, subjects randomised to placebo received BIIB037 low dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period.                                  |   |
| Reporting group title   | BIIB037 Late Start: High Dose (LTE Period)  |
| Reporting group description:<br>Following PC period, subjects randomised to placebo received BIIB037 high dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period.                                 |   |
| Reporting group title   | BIIB037 Early Start: Low Dose (LTE Period)  |
| Reporting group description:<br>Following PC period, subjects randomised to low dose BIIB037 continued to receive the same dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period.                |   |
| Reporting group title   | BIIB037 Early Start: High Dose (LTE Period) |
| Reporting group description:<br>Following PC period, subjects randomised to high dose BIIB037 continued to receive the same dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period.               |   |

### Primary: Change From Baseline in Clinical Dementia Rating Scale - Sum of Boxes (CDR-SB) Score at Week 78

|   |   |
|---|---|
| End point title   | Change From Baseline in Clinical Dementia Rating Scale - Sum of Boxes (CDR-SB) Score at Week 78 |
| End point description:<br>CDR-SB integrates assessments from 3 domains of cognition (memory, orientation, judgment/problem-solving) and 3 domains of function (community affairs, home/hobbies, personal care). Following caregiver interview and systematic patient examination, the rater assigns a score describing the subject's current performance level in each of these domains of life functioning. Prespecified severity anchors range from none = 0, questionable = 0.5, mild = 1, moderate = 2 to severe = 3 (the personal care domain omits the 0.5 score). "Sum of boxes" scoring methodology sums the score for each of the 6 domains and provides a value ranging from 0 to 18 that can change in increments of 0.5 or greater. Higher scores indicate greater disease severity. Mixed model for repeated measures (MMRM) analysis was used to analyse change from baseline in CDR-SB. A positive change from baseline indicates clinical decline. Intent-to-Treat (ITT) population. n=number of subjects analysed at specific timepoint. |   |
| End point type  | Primary   |
| End point timeframe:<br>Baseline, Week 78   |   |

| End point values                   | Placebo (PC Period) | BIIB037 Low Dose (PC Period) | BIIB037 High Dose (PC Period) |  |
|------------------------------------|---------------------|------------------------------|-------------------------------|--|
| Subject group type                 | Reporting group     | Reporting group              | Reporting group               |  |
| Number of subjects analysed        | 548                 | 543                          | 547                           |  |
| Units: score on a scale            |                     |                              |                               |  |
| arithmetic mean (standard error)   |                     |                              |                               |  |
| Change at Week 78 (n =288,290,299) | 1.74 ( $\pm$ 0.115) | 1.47 ( $\pm$ 0.116)          | 1.35 ( $\pm$ 0.115)           |  |

## Statistical analyses

| Statistical analysis title  | Placebo vs BIIB037 High Dose                        |
|---|---|
| Statistical analysis description:   |   |
| Adjusted mean for each treatment group (Placebo, BIIB037 Low Dose, BIIB037 High Dose), difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in CDR-SB as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit |   |
| Comparison groups   | Placebo (PC Period) v BIIB037 High Dose (PC Period) |
| Number of subjects included in analysis   | 1095  |
| Analysis specification  | Pre-specified                                       |
| Analysis type   | superiority   |
| P-value   | = 0.012   |
| Method  | MMRM  |
| Parameter estimate  | Difference  |
| Point estimate  | -0.39   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -0.694  |
| upper limit   | -0.086  |

| Statistical analysis title   | Placebo vs BIIB037 Low Dose                        |
|--|--|
| Statistical analysis description:  |  |
| Adjusted mean for each treatment group (Placebo, BIIB037 Low Dose, BIIB037 High Dose), difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in CDR-SB as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status. |  |
| Comparison groups  | Placebo (PC Period) v BIIB037 Low Dose (PC Period) |
| Number of subjects included in analysis  | 1091   |
| Analysis specification   | Pre-specified                                      |
| Analysis type  | superiority  |
| P-value  | = 0.0901   |
| Method   | mixed model for repeated measures (MMRM)           |
| Parameter estimate   | Difference   |
| Point estimate   | -0.26  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -0.569  |
| upper limit         | 0.041   |

## Secondary: Change From Baseline in Mini Mental State Examination (MMSE) score at Week 78

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Mini Mental State Examination (MMSE) score at Week 78 |
|-----------------|---|

### End point description:

The MMSE is a widely used performance-based test of global cognitive status. It consists of 11 tasks that assess orientation, word recall, attention and calculation, language abilities, and visuospatial functions. The scores from the 11 tests are combined to obtain the total score, which ranges from 0 to 30, with lower scores over time indicating increasing cognitive impairment. MMRM analysis was used to analyse change from baseline in MMSE. A negative change from baseline indicates clinical decline. ITT is defined as all randomised subjects who had received at least one dose of study treatment (Aducanumab or Placebo). Here, 'n' signifies number of subjects analysed at specific timepoint.

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

### End point timeframe:

Baseline, Week 78

| End point values                     | Placebo (PC Period) | BIIB037 Low Dose (PC Period) | BIIB037 High Dose (PC Period) |  |
|--------------------------------------|---------------------|------------------------------|-------------------------------|--|
| Subject group type                   | Reporting group     | Reporting group              | Reporting group               |  |
| Number of subjects analysed          | 548                 | 543                          | 547                           |  |
| Units: score on a scale              |                     |                              |                               |  |
| arithmetic mean (standard error)     |                     |                              |                               |  |
| Change at Week 78 (n =288, 293, 299) | -3.3 (± 0.22)       | -3.3 (± 0.22)                | -2.7 (± 0.21)                 |  |

## Statistical analyses

|                            |                              |
|----------------------------|------------------------------|
| Statistical analysis title | Placebo vs BIIB037 High Dose |
|----------------------------|------------------------------|

### Statistical analysis description:

Adjusted mean for each treatment group (Placebo, BIIB037 Low Dose, BIIB037 High Dose), difference from Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in MMSE as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline MMSE, baseline MMSE by visit interaction, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

|   |   |
|---|---|
| Comparison groups                       | Placebo (PC Period) v BIIB037 High Dose (PC Period) |
| Number of subjects included in analysis | 1095  |
| Analysis specification                  | Pre-specified                                       |
| Analysis type                           | superiority   |
| P-value                                 | = 0.0493  |
| Method                                  | MMRM  |
| Parameter estimate                      | Difference  |
| Point estimate                          | 0.6   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0       |
| upper limit         | 1.13    |

|                                   |                             |
|-----------------------------------|-----------------------------|
| <b>Statistical analysis title</b> | Placebo vs BIIB037 Low Dose |
|-----------------------------------|-----------------------------|

Statistical analysis description:

Adjusted mean for each treatment group (Placebo, BIIB037 Low Dose, BIIB037 High Dose), difference from Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in MMSE as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline MMSE, baseline MMSE by visit interaction, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

|   |  |
|---|--|
| Comparison groups                       | Placebo (PC Period) v BIIB037 Low Dose (PC Period) |
| Number of subjects included in analysis | 1091   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| P-value                                 | = 0.7578   |
| Method                                  | MMRM   |
| Parameter estimate                      | Difference   |
| Point estimate                          | -0.1   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -0.65  |
| upper limit                             | 0.48   |

### **Secondary: Change From Baseline in Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) (ADAS-Cog 13) at Week 78**

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) (ADAS-Cog 13) at Week 78 |
|-----------------|---|

End point description:

ADAS-Cog13 comprises both cognitive tasks and clinical ratings of cognitive performance. The scale items capture word recall, ability to follow commands, the ability to correctly copy or draw an image, naming, the ability to interact with everyday objects, orientation, word recognition, memory, comprehension of spoken language, word-finding, and language ability, with a measure for delayed word recall and concentration/distractibility. The total score ranges from 0 to 85. An increase in score over time indicates increasing cognitive impairment. MMRM analysis was used to analyse change from baseline in ADAS-Cog 13. A positive change from baseline indicates clinical decline. ITT is defined as all randomised subjects who had received at least one dose of study treatment (Aducanumab or Placebo). Here, 'n' signifies number of subjects analysed at specific timepoint.

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

End point timeframe:

Baseline, Week 78

| End point values                     | Placebo (PC Period)   | BIIB037 Low Dose (PC Period) | BIIB037 High Dose (PC Period) |  |
|--------------------------------------|-----------------------|------------------------------|-------------------------------|--|
| Subject group type                   | Reporting group       | Reporting group              | Reporting group               |  |
| Number of subjects analysed          | 548                   | 543                          | 547                           |  |
| Units: score on a scale              |                       |                              |                               |  |
| arithmetic mean (standard error)     |                       |                              |                               |  |
| Change at Week 78 (n =287, 289, 293) | 5.162 ( $\pm$ 0.4049) | 4.461 ( $\pm$ 0.4074)        | 3.763 ( $\pm$ 0.4036)         |  |

## Statistical analyses

| Statistical analysis title | Placebo vs BIIB037 Low Dose |
|----------------------------|-----------------------------|
|----------------------------|-----------------------------|

Statistical analysis description:

Adjusted mean for each treatment group(Placebo, BIIB037 Low Dose, BIIB037 High Dose),difference from Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in ADAS-Cog 13 as dependent variable and with fixed effects of treatment group,categorical visit,treatment-by-visit interaction,baseline ADAS-Cog 13,baseline ADAS-Cog 13 by visit interaction,baseline MMSE,AD symptomatic medication use at baseline,region,and laboratory ApoE status.

|   |  |
|---|--|
| Comparison groups                       | Placebo (PC Period) v BIIB037 Low Dose (PC Period) |
| Number of subjects included in analysis | 1091   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| P-value                                 | = 0.1962   |
| Method                                  | MMRM   |
| Parameter estimate                      | Difference   |
| Point estimate                          | -0.701   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -1.7649  |
| upper limit                             | 0.3627   |

| Statistical analysis title | Placebo vs BIIB037 High Dose |
|----------------------------|------------------------------|
|----------------------------|------------------------------|

Statistical analysis description:

Adjusted mean for each treatment group(Placebo, BIIB037 Low Dose, BIIB037 High Dose),difference from Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in ADAS-Cog 13 as dependent variable and with fixed effects of treatment group,categorical visit,treatment-by-visit interaction,baseline ADAS-Cog 13,baseline ADAS-Cog 13 by visit interaction,baseline MMSE,AD symptomatic medication use at baseline,region,and laboratory ApoE status.

|   |   |
|---|---|
| Comparison groups                       | Placebo (PC Period) v BIIB037 High Dose (PC Period) |
| Number of subjects included in analysis | 1095  |
| Analysis specification                  | Pre-specified                                       |
| Analysis type                           | superiority   |
| P-value                                 | = 0.0097  |
| Method                                  | MMRM  |
| Parameter estimate                      | Difference  |
| Point estimate                          | -1.4  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -2.4596 |
| upper limit         | -0.3396 |

## Secondary: Change From Baseline in Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) (ADCS-ADL-MCI) Score at Week 78

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) (ADCS-ADL-MCI) Score at Week 78 |
|-----------------|--|

### End point description:

The ADCS-ADL-MCI consists of 17 instrumental items (e.g., shopping, preparing meals, using household appliances) and 1 basic item (getting dressed). Ratings reflect caregiver observations about the patient's actual functioning over the previous month and provide an assessment of change in the functional state of the participant over time. The total score ranges from 0 to 53, with lower values over time reflecting functional deterioration. MMRM analysis was used to analyse change from baseline in ADAS-ADL-MCI. A negative change from baseline indicates clinical decline. ITT is defined as all randomised subjects who had received at least one dose of study treatment (Aducanumab or Placebo). Here, 'n' signifies number of subjects analysed at specific timepoint.

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

### End point timeframe:

Baseline, Week 78

| End point values                     | Placebo (PC Period) | BIIB037 Low Dose (PC Period) | BIIB037 High Dose (PC Period) |  |
|--------------------------------------|---------------------|------------------------------|-------------------------------|--|
| Subject group type                   | Reporting group     | Reporting group              | Reporting group               |  |
| Number of subjects analysed          | 548                 | 543                          | 547                           |  |
| Units: score on a scale              |                     |                              |                               |  |
| arithmetic mean (standard error)     |                     |                              |                               |  |
| Change at Week 78 (n =283, 286, 295) | -4.3 (± 0.38)       | -3.5 (± 0.38)                | -2.5 (± 0.38)                 |  |

## Statistical analyses

|                            |                              |
|----------------------------|------------------------------|
| Statistical analysis title | Placebo vs BIIB037 High Dose |
|----------------------------|------------------------------|

### Statistical analysis description:

Adjusted mean for each treatment group (Placebo, BIIB037 Low dose and BIIB037 High Dose), difference from Placebo, 95% CI and p-value at each time point were based on an MMRM model, with change from baseline in ADCSADL-MCI as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline ADCS-ADL-MCI, baseline ADCS-ADL-MCI by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

|                   |   |
|-------------------|---|
| Comparison groups | Placebo (PC Period) v BIIB037 High Dose (PC Period) |
|-------------------|---|

|   |               |
|---|---------------|
| Number of subjects included in analysis | 1095          |
| Analysis specification                  | Pre-specified |
| Analysis type                           | superiority   |
| P-value                                 | = 0.0006      |
| Method                                  | MMRM          |
| Parameter estimate                      | Difference    |
| Point estimate                          | 1.7           |
| Confidence interval                     |               |
| level                                   | 95 %          |
| sides                                   | 2-sided       |
| lower limit                             | 0.75          |
| upper limit                             | 2.74          |

|                                   |                             |
|-----------------------------------|-----------------------------|
| <b>Statistical analysis title</b> | Placebo vs BIIB037 Low Dose |
|-----------------------------------|-----------------------------|

Statistical analysis description:

Adjusted mean for each treatment group (Placebo, BIIB037 Low dose and BIIB037 High Dose), difference from Placebo, 95% CI and p-value at each time point were based on an MMRM model, with change from baseline in ADCSADL-MCI as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline ADCS-ADL-MCI, baseline ADCS-ADL-MCI by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

|   |  |
|---|--|
| Comparison groups                       | Placebo (PC Period) v BIIB037 Low Dose (PC Period) |
| Number of subjects included in analysis | 1091   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| P-value                                 | = 0.1515   |
| Method                                  | MMRM   |
| Parameter estimate                      | Difference   |
| Point estimate                          | 0.7  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -0.27  |
| upper limit                             | 1.73   |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From First Dose to End of Study (up to 4 years)

Adverse event reporting additional description:

Safety population was all randomised subjects who received at least one dose of study treatment. In PC period, 1 subject randomised to placebo, inadvertently received 1 or more doses of active treatment (Low Dose) during the PC period. For subjects affected, a subject was counted only once within each system organ class/preferred term/study period.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

### Reporting groups

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | BIIB037 Low Dose (PC Period) |
|-----------------------|------------------------------|

Reporting group description:

Subjects received a maximum of 20 infusions of BIIB037 low dose IV in PC period, administered approximately once every 4 weeks for up to approximately 1.5 years.

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Placebo (PC Period) |
|-----------------------|---------------------|

Reporting group description:

Subjects received a maximum of 20 infusions of BIIB037-matching placebo intravenously (IV) in PC period, administered approximately once every 4 weeks for up to approximately 1.5 years.

|                       |  |
|-----------------------|--|
| Reporting group title | BIIB037 Late Start: High Dose (LTE Period) |
|-----------------------|--|

Reporting group description:

Following PC period, subjects randomised to placebo received BIIB037 high dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period.

|                       |  |
|-----------------------|--|
| Reporting group title | BIIB037 Early Start: Low Dose (LTE Period) |
|-----------------------|--|

Reporting group description:

Following PC period, subjects randomised to low dose BIIB037 continued to receive the same dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period.

|                       |   |
|-----------------------|---|
| Reporting group title | BIIB037 Early Start: High Dose (LTE Period) |
|-----------------------|---|

Reporting group description:

Following PC period, subjects randomised to high dose BIIB037 continued to receive the same dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period.

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | BIIB037 High Dose (PC Period) |
|-----------------------|-------------------------------|

Reporting group description:

Subjects received a maximum of 20 infusions of BIIB037 high dose IV in PC period, administered approximately once every 4 weeks for up to approximately 1.5 years.

|                       |   |
|-----------------------|---|
| Reporting group title | BIIB037 Late Start: Low Dose (LTE period) |
|-----------------------|---|

Reporting group description:

Following PC period, subjects randomised to placebo received BIIB037 low dose, IV infusion, approximately every 4 weeks for up to 2 years in LTE period.

| Serious adverse events                            | BIIB037 Low Dose (PC Period) | Placebo (PC Period) | BIIB037 Late Start: High Dose (LTE Period) |
|---|------------------------------|---------------------|--|
| Total subjects affected by serious adverse events |                              |                     |  |
| subjects affected / exposed                       | 72 / 544 (13.24%)            | 81 / 547 (14.81%)   | 9 / 132 (6.82%)                            |
| number of deaths (all causes)                     | 0                            | 5                   | 0  |
| number of deaths resulting from                   |                              |                     |  |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| adverse events  |                 |                 |                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                 |                 |
| Adenocarcinoma of colon   |                 |                 |                 |
| subjects affected / exposed   | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 1 / 132 (0.76%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Adenocarcinoma pancreas   |                 |                 |                 |
| subjects affected / exposed   | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Basal cell carcinoma  |                 |                 |                 |
| subjects affected / exposed   | 2 / 544 (0.37%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Bladder papilloma   |                 |                 |                 |
| subjects affected / exposed   | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Breast cancer   |                 |                 |                 |
| subjects affected / exposed   | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Cholangiocarcinoma  |                 |                 |                 |
| subjects affected / exposed   | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Cholesteatoma   |                 |                 |                 |
| subjects affected / exposed   | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Diffuse large b-cell lymphoma                                       |                 |                 |                 |
| subjects affected / exposed   | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| Endometrial adenocarcinoma<br>subjects affected / exposed        | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (0.00%) |
| occurrences causally related to<br>treatment / all               | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Endometrial cancer<br>subjects affected / exposed                | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastric cancer<br>subjects affected / exposed                    | 1 / 544 (0.18%) | 1 / 547 (0.18%) | 0 / 132 (0.00%) |
| occurrences causally related to<br>treatment / all               | 1 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal neoplasm<br>subjects affected / exposed         | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Invasive ductal breast carcinoma<br>subjects affected / exposed  | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (0.00%) |
| occurrences causally related to<br>treatment / all               | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Invasive lobular breast carcinoma<br>subjects affected / exposed | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to<br>treatment / all               | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung adenocarcinoma stage iv<br>subjects affected / exposed      | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 1 / 132 (0.76%) |
| occurrences causally related to<br>treatment / all               | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung neoplasm malignant<br>subjects affected / exposed           | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to<br>treatment / all               | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Malignant melanoma   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Malignant melanoma in situ                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Medullary thyroid cancer                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Metastatic neoplasm                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Oesophageal carcinoma                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Ovarian cancer                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Pancreatic carcinoma metastatic                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Pleural mesothelioma                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Prostate cancer                                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 544 (0.37%) | 1 / 547 (0.18%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Prostatic adenoma                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Salivary gland cancer                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Small cell lung cancer                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Squamous cell carcinoma                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Squamous cell carcinoma of the oral cavity      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| T-cell lymphoma                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Thymoma malignant                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Vascular disorders                              |                 |                 |                 |
| Aortic aneurysm rupture                         |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Aortic stenosis                                      |                 |                 |                 |
| subjects affected / exposed                          | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Deep vein thrombosis                                 |                 |                 |                 |
| subjects affected / exposed                          | 1 / 544 (0.18%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Hypertension   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Hypertensive crisis                                  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 544 (0.00%) | 2 / 547 (0.37%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertensive urgency                                 |                 |                 |                 |
| subjects affected / exposed                          | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Hypotension  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| General disorders and administration site conditions |                 |                 |                 |
| Asthenia   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Chest pain   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Death   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Discomfort                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Gait disturbance                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 1 / 547 (0.18%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Medical device site joint pain                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Non-cardiac chest pain                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 2 / 547 (0.37%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyrexia   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Immune system disorders                         |                 |                 |                 |
| Hypersensitivity                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Reproductive system and breast disorders        |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Adnexa uteri cyst                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Benign prostatic hyperplasia                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Cervical polyp                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Gynaecomastia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Ovarian cyst                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Spermatic cord cyst                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Asthma  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Haemothorax                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Laryngeal oedema                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Lung perforation                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Pneumonia aspiration                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Pneumothorax                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Pulmonary embolism                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Respiratory failure                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psychiatric disorders                           |                 |                 |                 |
| Agitation                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 3 / 547 (0.55%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Anxiety   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Behaviour disorder                              |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Bipolar disorder                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Confusional state                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Delirium  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Delusion  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Depression                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 2 / 547 (0.37%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intentional self-injury                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Mania   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Mental status changes                           |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Neuropsychiatric symptoms                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Psychotic disorder                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Somatic symptom disorder                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Suicidal ideation                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Suicide attempt                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Investigations                                  |                 |                 |                 |
| Weight decreased                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Accident  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Accidental overdose                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Alcohol poisoning                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Animal attack                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Animal scratch                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Ankle fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 2 / 547 (0.37%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bone contusion                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac contusion                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Concussion                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Craniocerebral injury                           |                 |                 |                 |

|   |                 |                  |                 |
|---|-----------------|------------------|-----------------|
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%)  | 0 / 132 (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           |
| Epiphyseal fracture                             |                 |                  |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%)  | 0 / 132 (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           |
| Fall  |                 |                  |                 |
| subjects affected / exposed                     | 9 / 544 (1.65%) | 12 / 547 (2.19%) | 1 / 132 (0.76%) |
| occurrences causally related to treatment / all | 0 / 9           | 0 / 12           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Femoral neck fracture                           |                 |                  |                 |
| subjects affected / exposed                     | 2 / 544 (0.37%) | 3 / 547 (0.55%)  | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Foot fracture                                   |                 |                  |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%)  | 0 / 132 (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           |
| Gastrointestinal procedural complication        |                 |                  |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%)  | 0 / 132 (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           |
| Hand fracture                                   |                 |                  |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%)  | 0 / 132 (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           |
| Head injury                                     |                 |                  |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 1 / 547 (0.18%)  | 0 / 132 (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           |
| Hip fracture                                    |                 |                  |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Humerus fracture                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Joint dislocation                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Lower limb fracture                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Lumbar vertebral fracture                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Pelvic fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Pubis fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 1 / 132 (0.76%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary contusion                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Radius fracture                                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Rib fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 5 / 547 (0.91%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 5           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Road traffic accident                           |                 |                 |                 |
| subjects affected / exposed                     | 2 / 544 (0.37%) | 1 / 547 (0.18%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin laceration                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Skull fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Spinal fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Subdural haematoma                              |                 |                 |                 |
| subjects affected / exposed                     | 3 / 544 (0.55%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Thoracic vertebral fracture                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Upper limb fracture                             |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Wrist fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Cardiac disorders                               |                 |                 |                 |
| Acute coronary syndrome                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Acute left ventricular failure                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Acute myocardial infarction                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Angina unstable                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Aortic valve incompetence                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Atrial fibrillation                             |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 544 (0.00%) | 2 / 547 (0.37%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial flutter                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Atrioventricular block second degree            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Bradycardia                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Cardiac arrest                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 2 / 547 (0.37%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2           | 0 / 0           |
| Coronary artery disease                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Ischaemic cardiomyopathy                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Myocardial infarction                           |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed   | 1 / 544 (0.18%) | 2 / 547 (0.37%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all                                 | 0 / 1           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all                                      | 0 / 0           | 0 / 1           | 0 / 0           |
| Sinus bradycardia   |                 |                 |                 |
| subjects affected / exposed   | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Sinus node dysfunction  |                 |                 |                 |
| subjects affected / exposed   | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Sinus tachycardia   |                 |                 |                 |
| subjects affected / exposed   | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Stress cardiomyopathy   |                 |                 |                 |
| subjects affected / exposed   | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Supraventricular extrasystoles  |                 |                 |                 |
| subjects affected / exposed   | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all                                 | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                                      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders  |                 |                 |                 |
| Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits |                 |                 |                 |
| subjects affected / exposed   | 4 / 544 (0.74%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all                                 | 5 / 5           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                                      | 0 / 0           | 0 / 0           | 0 / 0           |
| Amyloid related imaging abnormality-oedema/effusion                             |                 |                 |                 |
| subjects affected / exposed   | 5 / 544 (0.92%) | 1 / 547 (0.18%) | 1 / 132 (0.76%) |
| occurrences causally related to treatment / all                                 | 6 / 6           | 1 / 1           | 1 / 1           |
| deaths causally related to treatment / all                                      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Carpal tunnel syndrome                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 1 / 132 (0.76%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebellar infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Cerebral haematoma                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Cerebral haemorrhage                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 1 / 132 (0.76%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebral infarction                             |                 |                 |                 |
| subjects affected / exposed                     | 2 / 544 (0.37%) | 2 / 547 (0.37%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebrovascular accident                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Dementia alzheimer's type                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 2 / 547 (0.37%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dizziness                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Embolic cerebral infarction                     |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Embolitic stroke                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Encephalopathy                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Focal dyscognitive seizures                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Generalised tonic-clonic seizure                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Guillain-barre syndrome                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Headache  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Intracranial venous sinus thrombosis            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Ischaemic stroke                                |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Lacunar infarction                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Loss of consciousness                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Memory impairment                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Metabolic encephalopathy                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Presyncope                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Quadriparesis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Seizure   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Sensorimotor disorder                           |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Superficial siderosis of central nervous system |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Syncope   |                 |                 |                 |
| subjects affected / exposed                     | 2 / 544 (0.37%) | 3 / 547 (0.55%) | 1 / 132 (0.76%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Thrombotic stroke                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Toxic encephalopathy                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Transient ischaemic attack                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Iron deficiency anaemia                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ear and labyrinth disorders                     |                 |                 |                 |
| Deafness bilateral                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Meniere's disease                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Vertigo   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye disorders                                   |                 |                 |                 |
| Age-related macular degeneration                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Cataract nuclear                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Retinal detachment                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Vitreous floaters                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Abdominal pain                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Acquired oesophageal web                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Barrett's oesophagus                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colitis   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Colitis ischaemic                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Constipation                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Diarrhoea                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 2 / 547 (0.37%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diverticular perforation                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Diverticulum intestinal haemorrhagic            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Duodenal ulcer perforation                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Dysphagia                                       |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Femoral hernia strangulated                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Gastrointestinal haemorrhage                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal necrosis                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Gastrooesophageal reflux disease                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Haemorrhoidal haemorrhage                       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 544 (0.37%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhoids                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Ileus   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Inguinal hernia                                 |                 |                 |                 |
| subjects affected / exposed                     | 2 / 544 (0.37%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intestinal obstruction                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Intestinal perforation                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Large intestine polyp                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 2 / 547 (0.37%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nausea  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Obstructive pancreatitis                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Pancreatitis acute                              |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Pneumoperitoneum                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Rectal prolapse                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Vomiting  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 2 / 547 (0.37%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Cholecystitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Cholecystitis acute                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 2 / 547 (0.37%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholelithiasis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Hepatitis acute                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Jaundice  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Acute kidney injury                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Calculus bladder                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Nephrolithiasis                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Prerenal failure                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal failure                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Urethral disorder                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Urethral stenosis                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary retention                               |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Endocrine disorders                             |                 |                 |                 |
| Inappropriate antidiuretic hormone secretion    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Arthritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Back pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Bursitis  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intervertebral disc protrusion                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Muscular weakness                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal pain                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Musculoskeletal stiffness                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 3 / 544 (0.55%) | 2 / 547 (0.37%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteonecrosis                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Rhabdomyolysis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Spinal osteoarthritis                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Vertebral foraminal stenosis                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| Appendicitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Bacterial infection                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Bronchitis                                      |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (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           |
| Cellulitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Cystitis klebsiella                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Erysipelas                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Gastroenteritis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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 viral                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Human anaplasmosis                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Lymphangitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Otitis media                                    |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 1 / 132 (0.76%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 544 (0.37%) | 2 / 547 (0.37%) | 1 / 132 (0.76%) |
| occurrences causally related to treatment / all | 1 / 2           | 1 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia bacterial                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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 influenzal                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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 respiratory syncytial viral           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Pulmonary sepsis                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Sepsis  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urosepsis                                       |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 547 (0.18%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| <b>Metabolism and nutrition disorders</b>       |                 |                 |                 |
| Dehydration                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Hyperglycaemia                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Hypoglycaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 0 / 132 (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           |
| Hyponatraemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 547 (0.00%) | 1 / 132 (0.76%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

| <b>Serious adverse events</b>  | BIIB037 Early Start:<br>Low Dose (LTE<br>Period) | BIIB037 Early Start:<br>High Dose (LTE<br>Period) | BIIB037 High Dose<br>(PC Period) |
|--|--|---|----------------------------------|
| Total subjects affected by serious adverse events                          |  |   |                                  |
| subjects affected / exposed  | 25 / 251 (9.96%)                                 | 25 / 257 (9.73%)                                  | 73 / 547 (13.35%)                |
| number of deaths (all causes)  | 3  | 0   | 6                                |
| number of deaths resulting from adverse events                             |  |   |                                  |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |  |   |                                  |
| Adenocarcinoma of colon  |  |   |                                  |
| subjects affected / exposed  | 1 / 251 (0.40%)                                  | 0 / 257 (0.00%)                                   | 1 / 547 (0.18%)                  |
| occurrences causally related to treatment / all                            | 0 / 1  | 0 / 0   | 0 / 1                            |
| deaths causally related to treatment / all                                 | 0 / 0  | 0 / 0   | 0 / 0                            |
| Adenocarcinoma pancreas  |  |   |                                  |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Basal cell carcinoma                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bladder papilloma                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Breast cancer                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Cholangiocarcinoma                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Cholesteatoma                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Diffuse large b-cell lymphoma                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Endometrial adenocarcinoma                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Endometrial cancer                              |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastric cancer                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal neoplasm                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Invasive ductal breast carcinoma                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Invasive lobular breast carcinoma               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Lung adenocarcinoma stage iv                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Lung neoplasm malignant                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Malignant melanoma                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Malignant melanoma in situ                      |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Medullary thyroid cancer                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Metastatic neoplasm                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Oesophageal carcinoma                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Ovarian cancer                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pancreatic carcinoma metastatic                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pleural mesothelioma                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Prostate cancer                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Prostatic adenoma                               |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Salivary gland cancer                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Small cell lung cancer                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Squamous cell carcinoma                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Squamous cell carcinoma of the oral cavity      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| T-cell lymphoma                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Thymoma malignant                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Vascular disorders                              |                 |                 |                 |
| Aortic aneurysm rupture                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Aortic stenosis                                 |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Deep vein thrombosis                                 |                 |                 |                 |
| subjects affected / exposed                          | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Hypertension   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Hypertensive crisis                                  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Hypertensive urgency                                 |                 |                 |                 |
| subjects affected / exposed                          | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypotension  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |
| Asthenia   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Chest pain   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 251 (0.40%) | 1 / 257 (0.39%) | 0 / 547 (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           |
| Death  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Discomfort                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Gait disturbance                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 2 / 257 (0.78%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Medical device site joint pain                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Non-cardiac chest pain                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 2 / 547 (0.37%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyrexia   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Immune system disorders                         |                 |                 |                 |
| Hypersensitivity                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Reproductive system and breast disorders        |                 |                 |                 |
| Adnexa uteri cyst                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Benign prostatic hyperplasia                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cervical polyp                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gynaecomastia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Ovarian cyst                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Spermatic cord cyst                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Asthma  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 1 / 257 (0.39%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemothorax                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 1 / 257 (0.39%) | 0 / 547 (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           |
| Laryngeal oedema                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Lung perforation                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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 aspiration                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Pneumothorax                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 1 / 257 (0.39%) | 0 / 547 (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           |
| Pulmonary embolism                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 2 / 547 (0.37%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Respiratory failure                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psychiatric disorders                           |                 |                 |                 |
| Agitation                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Anxiety   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 1 / 257 (0.39%) | 0 / 547 (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           |
| Behaviour disorder                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 1 / 257 (0.39%) | 0 / 547 (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           |
| Bipolar disorder                                |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Confusional state                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Delirium  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Delusion  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Depression                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intentional self-injury                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Mania   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mental status changes                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Neuropsychiatric symptoms                       |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Psychotic disorder                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Somatic symptom disorder                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Suicidal ideation                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Suicide attempt                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Investigations                                  |                 |                 |                 |
| Weight decreased                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Accident  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 1 / 257 (0.39%) | 0 / 547 (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           |
| Accidental overdose                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Alcohol poisoning                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Animal attack                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Animal scratch                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Ankle fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Bone contusion                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac contusion                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Concussion                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Craniocerebral injury                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Epiphyseal fracture                             |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Fall  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 6 / 257 (2.33%) | 4 / 547 (0.73%) |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 6           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Femoral neck fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Foot fracture                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal procedural complication        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hand fracture                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Head injury                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Hip fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 2 / 257 (0.78%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Humerus fracture                                |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Joint dislocation                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lower limb fracture                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Lumbar vertebral fracture                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Pelvic fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Pubis fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary contusion                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Radius fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rib fracture                                    |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 251 (0.00%) | 1 / 257 (0.39%) | 0 / 547 (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           |
| Road traffic accident                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Skin laceration                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Skull fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Spinal fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Subdural haematoma                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 1 / 257 (0.39%) | 2 / 547 (0.37%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Thoracic vertebral fracture                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Upper limb fracture                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Wrist fracture                                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 251 (0.00%) | 1 / 257 (0.39%) | 0 / 547 (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           |
| Cardiac disorders                               |                 |                 |                 |
| Acute coronary syndrome                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Acute left ventricular failure                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Acute myocardial infarction                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 1 / 257 (0.39%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Angina unstable                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Aortic valve incompetence                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Atrial fibrillation                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Atrial flutter                                  |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Atrioventricular block second degree            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bradycardia                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac arrest                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 2 / 547 (0.37%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 2           |
| Cardiac failure congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Coronary artery disease                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 2 / 257 (0.78%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ischaemic cardiomyopathy                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Myocardial infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Sinus bradycardia                               |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed   | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all                                 | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                                      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sinus node dysfunction  |                 |                 |                 |
| subjects affected / exposed   | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all                                 | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                                      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sinus tachycardia   |                 |                 |                 |
| subjects affected / exposed   | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Stress cardiomyopathy   |                 |                 |                 |
| subjects affected / exposed   | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all                                 | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                                      | 0 / 0           | 0 / 0           | 0 / 0           |
| Supraventricular extrasystoles  |                 |                 |                 |
| subjects affected / exposed   | 0 / 251 (0.00%) | 1 / 257 (0.39%) | 0 / 547 (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           |
| Nervous system disorders  |                 |                 |                 |
| Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits |                 |                 |                 |
| subjects affected / exposed   | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 2 / 547 (0.37%) |
| occurrences causally related to treatment / all                                 | 0 / 0           | 0 / 0           | 4 / 4           |
| deaths causally related to treatment / all                                      | 0 / 0           | 0 / 0           | 0 / 0           |
| Amyloid related imaging abnormality-oedema/effusion                             |                 |                 |                 |
| subjects affected / exposed   | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 8 / 547 (1.46%) |
| occurrences causally related to treatment / all                                 | 0 / 0           | 0 / 0           | 8 / 8           |
| deaths causally related to treatment / all                                      | 0 / 0           | 0 / 0           | 0 / 0           |
| Carpal tunnel syndrome  |                 |                 |                 |
| subjects affected / exposed   | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Cerebellar infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 2           |
| Cerebral haematoma                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Cerebral haemorrhage                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebral infarction                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Cerebrovascular accident                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Dementia alzheimer's type                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Dizziness                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Embolic cerebral infarction                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Embolic stroke                                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 251 (0.00%) | 1 / 257 (0.39%) | 0 / 547 (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           |
| Encephalopathy                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Focal dyscognitive seizures                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Generalised tonic-clonic seizure                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Guillain-barre syndrome                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 1 / 257 (0.39%) | 0 / 547 (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           |
| Headache  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Intracranial venous sinus thrombosis            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ischaemic stroke                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 1 / 257 (0.39%) | 0 / 547 (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           |
| Lacunar infarction                              |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Loss of consciousness                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Memory impairment                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Metabolic encephalopathy                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Presyncope                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Quadriparesis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Seizure   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sensorimotor disorder                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Superficial siderosis of central nervous system |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 3 / 547 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 4 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Syncope   |                 |                 |                 |
| subjects affected / exposed                     | 2 / 251 (0.80%) | 2 / 257 (0.78%) | 4 / 547 (0.73%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 4           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Thrombotic stroke                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Toxic encephalopathy                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Transient ischaemic attack                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 1 / 257 (0.39%) | 2 / 547 (0.37%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Iron deficiency anaemia                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Ear and labyrinth disorders                     |                 |                 |                 |
| Deafness bilateral                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Meniere's disease                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Vertigo   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye disorders                                   |                 |                 |                 |
| Age-related macular degeneration                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Cataract nuclear                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Retinal detachment                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 1 / 257 (0.39%) | 0 / 547 (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           |
| Vitreous floaters                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Abdominal pain                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Acquired oesophageal web                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Barrett's oesophagus                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Colitis   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Colitis ischaemic                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Constipation                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diarrhoea                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Diverticular perforation                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Diverticulum intestinal haemorrhagic            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Duodenal ulcer perforation                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dysphagia                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Femoral hernia strangulated                     |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Gastritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 2 / 547 (0.37%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal haemorrhage                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal necrosis                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Gastrooesophageal reflux disease                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Haemorrhoidal haemorrhage                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Haemorrhoids                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 1 / 257 (0.39%) | 0 / 547 (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           |
| Ileus   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Inguinal hernia                                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 3 / 547 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intestinal obstruction                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intestinal perforation                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 1 / 257 (0.39%) | 0 / 547 (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           |
| Large intestine polyp                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nausea  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Obstructive pancreatitis                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pancreatitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pancreatitis acute                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumoperitoneum                                |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Rectal prolapse                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vomiting  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Cholecystitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Cholecystitis acute                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Cholelithiasis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatitis acute                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Jaundice  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Acute kidney injury                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Calculus bladder                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Nephrolithiasis                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Prerenal failure                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal failure                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Urethral disorder                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Urethral stenosis                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary retention                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Endocrine disorders                             |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Inappropriate antidiuretic hormone secretion    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Arthritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Back pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 1 / 257 (0.39%) | 0 / 547 (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           |
| Bursitis  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intervertebral disc protrusion                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Muscular weakness                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal pain                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 1 / 257 (0.39%) | 0 / 547 (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           |
| Musculoskeletal stiffness                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteonecrosis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rhabdomyolysis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Spinal osteoarthritis                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Vertebral foraminal stenosis                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Infections and infestations                     |                 |                 |                 |
| Appendicitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bacterial infection                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Bronchitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cellulitis                                      |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 2 / 547 (0.37%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cystitis klebsiella                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Erysipelas                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Gastroenteritis viral                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 1 / 257 (0.39%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Human anaplasmosis                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lymphangitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Otitis media                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia                                       |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia bacterial                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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 influenzal                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 1 / 257 (0.39%) | 0 / 547 (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           |
| Pneumonia respiratory syncytial viral           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Pulmonary sepsis                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Sepsis  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 1 / 257 (0.39%) | 2 / 547 (0.37%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 251 (0.40%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urosepsis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Dehydration                                     |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperglycaemia                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Hypoglycaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 0 / 547 (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           |
| Hyponatraemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 251 (0.00%) | 0 / 257 (0.00%) | 1 / 547 (0.18%) |
| 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>                                       | BIIB037 Late Start:<br>Low Dose (LTE<br>period) |  |  |
| Total subjects affected by serious adverse events                   |   |  |  |
| subjects affected / exposed   | 15 / 131 (11.45%)                               |  |  |
| number of deaths (all causes)                                       | 0   |  |  |
| number of deaths resulting from adverse events                      |   |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |  |  |
| Adenocarcinoma of colon   |   |  |  |
| subjects affected / exposed   | 1 / 131 (0.76%)                                 |  |  |
| occurrences causally related to treatment / all                     | 0 / 1   |  |  |
| deaths causally related to treatment / all                          | 0 / 0   |  |  |
| Adenocarcinoma pancreas   |   |  |  |
| subjects affected / exposed   | 1 / 131 (0.76%)                                 |  |  |
| occurrences causally related to treatment / all                     | 0 / 1   |  |  |
| deaths causally related to treatment / all                          | 0 / 0   |  |  |
| Basal cell carcinoma  |   |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bladder papilloma                               |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Breast cancer                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cholangiocarcinoma                              |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cholesteatoma                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Diffuse large b-cell lymphoma                   |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Endometrial adenocarcinoma                      |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Endometrial cancer                              |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastric cancer                                  |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal neoplasm                       |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Invasive ductal breast carcinoma                |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Invasive lobular breast carcinoma               |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lung adenocarcinoma stage iv                    |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lung neoplasm malignant                         |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Malignant melanoma                              |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Malignant melanoma in situ                      |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Medullary thyroid cancer                        |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metastatic neoplasm                             |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Oesophageal carcinoma                           |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ovarian cancer                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pancreatic carcinoma metastatic                 |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pleural mesothelioma                            |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Prostate cancer                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Prostatic adenoma                               |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Salivary gland cancer                           |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Small cell lung cancer                          |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Squamous cell carcinoma                         |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Squamous cell carcinoma of the oral cavity      |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| T-cell lymphoma                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Thymoma malignant                               |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vascular disorders                              |                 |  |  |
| Aortic aneurysm rupture                         |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Aortic stenosis                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Deep vein thrombosis                            |                 |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                          | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Hypertension   |                 |  |  |
| subjects affected / exposed                          | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Hypertensive crisis                                  |                 |  |  |
| subjects affected / exposed                          | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Hypertensive urgency                                 |                 |  |  |
| subjects affected / exposed                          | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Hypotension  |                 |  |  |
| subjects affected / exposed                          | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Asthenia   |                 |  |  |
| subjects affected / exposed                          | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Chest pain   |                 |  |  |
| subjects affected / exposed                          | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Death  |                 |  |  |
| subjects affected / exposed                          | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Discomfort   |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gait disturbance                                |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Medical device site joint pain                  |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Non-cardiac chest pain                          |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pyrexia   |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Immune system disorders                         |                 |  |  |
| Hypersensitivity                                |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Reproductive system and breast disorders        |                 |  |  |
| Adnexa uteri cyst                               |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Benign prostatic hyperplasia                    |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Cervical polyp                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gynaecomastia                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 131 (0.76%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ovarian cyst                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Spermatic cord cyst                             |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Asthma  |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haemothorax                                     |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Laryngeal oedema                                |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lung perforation                                |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| Pneumonia aspiration                            |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumothorax                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary embolism                              |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory failure                             |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychiatric disorders                           |                 |  |  |
| Agitation                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Anxiety   |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Behaviour disorder                              |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bipolar disorder                                |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Confusional state                               |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Delirium  |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Delusion  |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Depression                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intentional self-injury                         |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Mania   |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Mental status changes                           |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Neuropsychiatric symptoms                       |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychotic disorder                              |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Somatic symptom disorder                        |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Suicidal ideation                               |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Suicide attempt                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Investigations                                  |                 |  |  |
| Weight decreased                                |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| Accident  |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Accidental overdose                             |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Alcohol poisoning                               |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| Animal attack                                   |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Animal scratch                                  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Ankle fracture                                  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Bone contusion                                  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cardiac contusion                               |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Concussion                                      |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Craniocerebral injury                           |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Epiphyseal fracture                             |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Fall  |                 |  |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 2 / 131 (1.53%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Femoral neck fracture                           |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Foot fracture                                   |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gastrointestinal procedural complication        |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Hand fracture                                   |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Head injury                                     |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Hip fracture                                    |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Humerus fracture                                |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Joint dislocation                               |                 |  |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 131 (0.76%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Lower limb fracture                             |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Lumbar vertebral fracture                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 131 (0.76%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pelvic fracture                                 |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pubis fracture                                  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pulmonary contusion                             |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Radius fracture                                 |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Rib fracture                                    |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Road traffic accident                           |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skin laceration                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skull fracture                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 131 (0.76%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Spinal fracture                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Subdural haematoma                              |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Thoracic vertebral fracture                     |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Upper limb fracture                             |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Wrist fracture                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Acute coronary syndrome                         |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Acute left ventricular failure                  |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Acute myocardial infarction                     |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Angina pectoris                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Angina unstable                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Aortic valve incompetence                       |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atrial fibrillation                             |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atrial flutter                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atrioventricular block second degree            |                 |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bradycardia                                     |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac arrest                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac failure congestive                      |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Coronary artery disease                         |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ischaemic cardiomyopathy                        |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Myocardial infarction                           |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Sinus bradycardia                               |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Sinus node dysfunction                          |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed   | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all                                 | 0 / 0           |  |  |
| deaths causally related to treatment / all                                      | 0 / 0           |  |  |
| Sinus tachycardia   |                 |  |  |
| subjects affected / exposed   | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all                                 | 0 / 0           |  |  |
| deaths causally related to treatment / all                                      | 0 / 0           |  |  |
| Stress cardiomyopathy   |                 |  |  |
| subjects affected / exposed   | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all                                 | 0 / 0           |  |  |
| deaths causally related to treatment / all                                      | 0 / 0           |  |  |
| Supraventricular extrasystoles  |                 |  |  |
| subjects affected / exposed   | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all                                 | 0 / 0           |  |  |
| deaths causally related to treatment / all                                      | 0 / 0           |  |  |
| Nervous system disorders  |                 |  |  |
| Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits |                 |  |  |
| subjects affected / exposed   | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all                                 | 0 / 0           |  |  |
| deaths causally related to treatment / all                                      | 0 / 0           |  |  |
| Amyloid related imaging abnormality-oedema/effusion                             |                 |  |  |
| subjects affected / exposed   | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all                                 | 0 / 0           |  |  |
| deaths causally related to treatment / all                                      | 0 / 0           |  |  |
| Carpal tunnel syndrome  |                 |  |  |
| subjects affected / exposed   | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all                                 | 0 / 0           |  |  |
| deaths causally related to treatment / all                                      | 0 / 0           |  |  |
| Cerebellar infarction   |                 |  |  |
| subjects affected / exposed   | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all                                 | 0 / 0           |  |  |
| deaths causally related to treatment / all                                      | 0 / 0           |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| Cerebral haematoma                              |                 |  |  |  |
| subjects affected / exposed                     | 1 / 131 (0.76%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cerebral haemorrhage                            |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cerebral infarction                             |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cerebrovascular accident                        |                 |  |  |  |
| subjects affected / exposed                     | 1 / 131 (0.76%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Dementia alzheimer's type                       |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Dizziness                                       |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Embolic cerebral infarction                     |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Embolic stroke                                  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Encephalopathy                                  |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Focal dyscognitive seizures                     |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Generalised tonic-clonic seizure                |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Guillain-barre syndrome                         |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Headache  |                 |  |  |
| subjects affected / exposed                     | 1 / 131 (0.76%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intracranial venous sinus thrombosis            |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ischaemic stroke                                |                 |  |  |
| subjects affected / exposed                     | 1 / 131 (0.76%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lacunar infarction                              |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Loss of consciousness                           |                 |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Memory impairment                               |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Metabolic encephalopathy                        |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Presyncope                                      |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Quadriparesis                                   |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Seizure   |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Sensorimotor disorder                           |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Superficial siderosis of central nervous system |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Syncope   |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Thrombotic stroke                               |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Toxic encephalopathy                            |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Transient ischaemic attack                      |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood and lymphatic system disorders            |                 |  |  |
| Iron deficiency anaemia                         |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ear and labyrinth disorders                     |                 |  |  |
| Deafness bilateral                              |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Meniere's disease                               |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vertigo   |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Eye disorders                                   |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Age-related macular degeneration<br>subjects affected / exposed | 0 / 131 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           |  |  |
| Cataract nuclear<br>subjects affected / exposed                 | 0 / 131 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           |  |  |
| Retinal detachment<br>subjects affected / exposed               | 0 / 131 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           |  |  |
| Vitreous floaters<br>subjects affected / exposed                | 1 / 131 (0.76%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           |  |  |
| Gastrointestinal disorders                                      |                 |  |  |
| Abdominal pain<br>subjects affected / exposed                   | 1 / 131 (0.76%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           |  |  |
| Acquired oesophageal web<br>subjects affected / exposed         | 0 / 131 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           |  |  |
| Barrett's oesophagus<br>subjects affected / exposed             | 0 / 131 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           |  |  |
| Colitis<br>subjects affected / exposed                          | 0 / 131 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           |  |  |
| Colitis ischaemic   |                 |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Constipation                                    |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Diarrhoea                                       |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Diverticular perforation                        |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Diverticulum intestinal haemorrhagic            |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Duodenal ulcer perforation                      |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Dysphagia                                       |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Femoral hernia strangulated                     |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gastritis                                       |                 |  |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal haemorrhage                    |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal necrosis                       |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrooesophageal reflux disease                |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haemorrhoidal haemorrhage                       |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haemorrhoids                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ileus   |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Inguinal hernia                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intestinal obstruction                          |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intestinal perforation                          |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Large intestine polyp                           |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nausea  |                 |  |  |
| subjects affected / exposed                     | 1 / 131 (0.76%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Obstructive pancreatitis                        |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pancreatitis                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pancreatitis acute                              |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumoperitoneum                                |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Rectal prolapse                                 |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vomiting  |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| Cholecystitis                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 131 (0.76%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cholecystitis acute                             |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cholelithiasis                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatitis acute                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 131 (0.76%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Jaundice  |                 |  |  |
| subjects affected / exposed                     | 1 / 131 (0.76%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Acute kidney injury                             |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Calculus bladder                                |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nephrolithiasis                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 131 (0.76%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Prerenal failure                                |                 |  |  |
| subjects affected / exposed                     | 1 / 131 (0.76%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal failure                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urethral disorder                               |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urethral stenosis                               |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urinary retention                               |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Endocrine disorders                             |                 |  |  |
| Inappropriate antidiuretic hormone secretion    |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| Arthritis                                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 131 (0.76%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Back pain                                       |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Bursitis  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Intervertebral disc protrusion                  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Muscular weakness                               |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Musculoskeletal pain                            |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Musculoskeletal stiffness                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 131 (0.76%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Osteoarthritis                                  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Osteonecrosis                                   |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 131 (0.76%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Rhabdomyolysis                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Spinal osteoarthritis                           |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vertebral foraminal stenosis                    |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Appendicitis                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bacterial infection                             |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bronchitis                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cellulitis                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cystitis klebsiella                             |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Erysipelas                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastroenteritis                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastroenteritis viral                           |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Human anaplasmosis                              |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lymphangitis                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Otitis media                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 131 (0.76%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia bacterial                             |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 131 (0.76%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia influenzal                            |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia respiratory syncytial viral           |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary sepsis                                |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Sepsis  |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urinary tract infection                         |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urosepsis                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (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 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hyperglycaemia                                  |                 |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypoglycaemia                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hyponatraemia                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 131 (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: 5 %

| <b>Non-serious adverse events</b>   | BIIB037 Low Dose<br>(PC Period) | Placebo (PC Period) | BIIB037 Late Start:<br>High Dose (LTE<br>Period) |
|---|---------------------------------|---------------------|--|
| Total subjects affected by non-serious adverse events                           |                                 |                     |  |
| subjects affected / exposed   | 385 / 544 (70.77%)              | 353 / 547 (64.53%)  | 56 / 132 (42.42%)                                |
| Injury, poisoning and procedural complications                                  |                                 |                     |  |
| Fall  |                                 |                     |  |
| subjects affected / exposed   | 59 / 544 (10.85%)               | 62 / 547 (11.33%)   | 7 / 132 (5.30%)                                  |
| occurrences (all)   | 82                              | 86                  | 8  |
| Nervous system disorders  |                                 |                     |  |
| Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits |                                 |                     |  |
| subjects affected / exposed   | 86 / 544 (15.81%)               | 37 / 547 (6.76%)    | 11 / 132 (8.33%)                                 |
| occurrences (all)   | 114                             | 42                  | 17   |
| Amyloid related imaging abnormality-oedema/effusion                             |                                 |                     |  |
| subjects affected / exposed   | 138 / 544 (25.37%)              | 12 / 547 (2.19%)    | 31 / 132 (23.48%)                                |
| occurrences (all)   | 199                             | 13                  | 46   |
| Dizziness   |                                 |                     |  |
| subjects affected / exposed   | 42 / 544 (7.72%)                | 43 / 547 (7.86%)    | 0 / 132 (0.00%)                                  |
| occurrences (all)   | 55                              | 46                  | 0  |
| Headache  |                                 |                     |  |

|  |                           |                          |                         |
|--|---------------------------|--------------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)   | 109 / 544 (20.04%)<br>196 | 84 / 547 (15.36%)<br>116 | 13 / 132 (9.85%)<br>16  |
| Superficial siderosis of central<br>nervous system<br>subjects affected / exposed<br>occurrences (all)                 | 51 / 544 (9.38%)<br>64    | 14 / 547 (2.56%)<br>18   | 17 / 132 (12.88%)<br>23 |
| General disorders and administration<br>site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all) | 27 / 544 (4.96%)<br>29    | 37 / 547 (6.76%)<br>44   | 0 / 132 (0.00%)<br>0    |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                            | 38 / 544 (6.99%)<br>47    | 29 / 547 (5.30%)<br>31   | 7 / 132 (5.30%)<br>8    |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 29 / 544 (5.33%)<br>40    | 27 / 547 (4.94%)<br>35   | 0 / 132 (0.00%)<br>0    |
| Respiratory, thoracic and mediastinal<br>disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)        | 24 / 544 (4.41%)<br>28    | 28 / 547 (5.12%)<br>31   | 4 / 132 (3.03%)<br>4    |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)                                   | 30 / 544 (5.51%)<br>30    | 21 / 547 (3.84%)<br>24   | 0 / 132 (0.00%)<br>0    |
| Confusional state<br>subjects affected / exposed<br>occurrences (all)  | 16 / 544 (2.94%)<br>18    | 15 / 547 (2.74%)<br>17   | 0 / 132 (0.00%)<br>0    |
| Depression<br>subjects affected / exposed<br>occurrences (all)   | 29 / 544 (5.33%)<br>31    | 28 / 547 (5.12%)<br>28   | 0 / 132 (0.00%)<br>0    |
| Musculoskeletal and connective tissue<br>disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)   | 17 / 544 (3.13%)<br>20    | 31 / 547 (5.67%)<br>35   | 0 / 132 (0.00%)<br>0    |
| Back pain  |                           |                          |                         |

|  |                        |                        |                      |
|--|------------------------|------------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 38 / 544 (6.99%)<br>39 | 36 / 547 (6.58%)<br>40 | 3 / 132 (2.27%)<br>3 |
| Infections and infestations                      |                        |                        |                      |
| Nasopharyngitis                                  |                        |                        |                      |
| subjects affected / exposed                      | 71 / 544 (13.05%)      | 91 / 547 (16.64%)      | 7 / 132 (5.30%)      |
| occurrences (all)                                | 87                     | 124                    | 12                   |
| Upper respiratory tract infection                |                        |                        |                      |
| subjects affected / exposed                      | 42 / 544 (7.72%)       | 41 / 547 (7.50%)       | 2 / 132 (1.52%)      |
| occurrences (all)                                | 55                     | 52                     | 2                    |
| Urinary tract infection                          |                        |                        |                      |
| subjects affected / exposed                      | 39 / 544 (7.17%)       | 36 / 547 (6.58%)       | 0 / 132 (0.00%)      |
| occurrences (all)                                | 55                     | 47                     | 0                    |

| <b>Non-serious adverse events</b>   | BIIB037 Early Start:<br>Low Dose (LTE<br>Period) | BIIB037 Early Start:<br>High Dose (LTE<br>Period) | BIIB037 High Dose<br>(PC Period) |
|---|--|---|----------------------------------|
| Total subjects affected by non-serious<br>adverse events                              |  |   |                                  |
| subjects affected / exposed   | 87 / 251 (34.66%)                                | 107 / 257 (41.63%)                                | 428 / 547 (78.24%)               |
| Injury, poisoning and procedural<br>complications                                     |  |   |                                  |
| Fall  |  |   |                                  |
| subjects affected / exposed   | 15 / 251 (5.98%)                                 | 32 / 257 (12.45%)                                 | 73 / 547 (13.35%)                |
| occurrences (all)   | 16   | 49  | 109                              |
| Nervous system disorders  |  |   |                                  |
| Amyloid related imaging<br>abnormality-microhaemorrhages and<br>haemosiderin deposits |  |   |                                  |
| subjects affected / exposed   | 12 / 251 (4.78%)                                 | 21 / 257 (8.17%)                                  | 106 / 547 (19.38%)               |
| occurrences (all)   | 15   | 24  | 160                              |
| Amyloid related imaging<br>abnormality-oedema/effusion                                |  |   |                                  |
| subjects affected / exposed   | 11 / 251 (4.38%)                                 | 22 / 257 (8.56%)                                  | 183 / 547 (33.46%)               |
| occurrences (all)   | 13   | 27  | 298                              |
| Dizziness   |  |   |                                  |
| subjects affected / exposed   | 0 / 251 (0.00%)                                  | 0 / 257 (0.00%)                                   | 55 / 547 (10.05%)                |
| occurrences (all)   | 0  | 0   | 78                               |
| Headache  |  |   |                                  |
| subjects affected / exposed   | 20 / 251 (7.97%)                                 | 19 / 257 (7.39%)                                  | 107 / 547 (19.56%)               |
| occurrences (all)   | 35   | 25  | 167                              |
| Superficial siderosis of central<br>nervous system                                    |  |   |                                  |

|   |  |  |  |
|---|--|--|--|
| subjects affected / exposed<br>occurrences (all)  | 4 / 251 (1.59%)<br>5   | 10 / 257 (3.89%)<br>13   | 71 / 547 (12.98%)<br>92  |
| General disorders and administration<br>site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all)  | 0 / 251 (0.00%)<br>0   | 0 / 257 (0.00%)<br>0   | 34 / 547 (6.22%)<br>43   |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Nausea<br>subjects affected / exposed<br>occurrences (all)   | 9 / 251 (3.59%)<br>10<br><br>0 / 251 (0.00%)<br>0                            | 6 / 257 (2.33%)<br>6<br><br>0 / 257 (0.00%)<br>0                             | 42 / 547 (7.68%)<br>58<br><br>31 / 547 (5.67%)<br>35                               |
| Respiratory, thoracic and mediastinal<br>disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)   | 7 / 251 (2.79%)<br>7   | 14 / 257 (5.45%)<br>15   | 33 / 547 (6.03%)<br>36   |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)<br><br>Confusional state<br>subjects affected / exposed<br>occurrences (all)<br><br>Depression<br>subjects affected / exposed<br>occurrences (all) | 0 / 251 (0.00%)<br>0<br><br>0 / 251 (0.00%)<br>0<br><br>0 / 251 (0.00%)<br>0 | 0 / 257 (0.00%)<br>0<br><br>0 / 257 (0.00%)<br>0<br><br>0 / 257 (0.00%)<br>0 | 19 / 547 (3.47%)<br>22<br><br>28 / 547 (5.12%)<br>35<br><br>23 / 547 (4.20%)<br>23 |
| Musculoskeletal and connective tissue<br>disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Back pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 251 (0.00%)<br>0<br><br>9 / 251 (3.59%)<br>9                             | 0 / 257 (0.00%)<br>0<br><br>10 / 257 (3.89%)<br>13                           | 34 / 547 (6.22%)<br>40<br><br>42 / 547 (7.68%)<br>45                               |
| Infections and infestations   |  |  |  |

|                                   |                  |                  |                   |
|-----------------------------------|------------------|------------------|-------------------|
| Nasopharyngitis                   |                  |                  |                   |
| subjects affected / exposed       | 18 / 251 (7.17%) | 19 / 257 (7.39%) | 89 / 547 (16.27%) |
| occurrences (all)                 | 24               | 24               | 129               |
| Upper respiratory tract infection |                  |                  |                   |
| subjects affected / exposed       | 13 / 251 (5.18%) | 11 / 257 (4.28%) | 38 / 547 (6.95%)  |
| occurrences (all)                 | 13               | 11               | 42                |
| Urinary tract infection           |                  |                  |                   |
| subjects affected / exposed       | 0 / 251 (0.00%)  | 0 / 257 (0.00%)  | 29 / 547 (5.30%)  |
| occurrences (all)                 | 0                | 0                | 37                |

|   |   |  |  |
|---|---|--|--|
| <b>Non-serious adverse events</b>   | BIIB037 Late Start:<br>Low Dose (LTE<br>period) |  |  |
| Total subjects affected by non-serious<br>adverse events                              |   |  |  |
| subjects affected / exposed   | 55 / 131 (41.98%)                               |  |  |
| Injury, poisoning and procedural<br>complications                                     |   |  |  |
| Fall  |   |  |  |
| subjects affected / exposed   | 13 / 131 (9.92%)                                |  |  |
| occurrences (all)   | 18  |  |  |
| Nervous system disorders  |   |  |  |
| Amyloid related imaging<br>abnormality-microhaemorrhages and<br>haemosiderin deposits |   |  |  |
| subjects affected / exposed   | 18 / 131 (13.74%)                               |  |  |
| occurrences (all)   | 22  |  |  |
| Amyloid related imaging<br>abnormality-oedema/effusion                                |   |  |  |
| subjects affected / exposed   | 23 / 131 (17.56%)                               |  |  |
| occurrences (all)   | 29  |  |  |
| Dizziness   |   |  |  |
| subjects affected / exposed   | 0 / 131 (0.00%)                                 |  |  |
| occurrences (all)   | 0   |  |  |
| Headache  |   |  |  |
| subjects affected / exposed   | 10 / 131 (7.63%)                                |  |  |
| occurrences (all)   | 19  |  |  |
| Superficial siderosis of central<br>nervous system                                    |   |  |  |
| subjects affected / exposed   | 13 / 131 (9.92%)                                |  |  |
| occurrences (all)   | 14  |  |  |
| General disorders and administration<br>site conditions                               |   |  |  |

|   |  |  |  |
|---|--|--|--|
| Fatigue<br>subjects affected / exposed<br>occurrences (all)   | 0 / 131 (0.00%)<br>0   |  |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Nausea<br>subjects affected / exposed<br>occurrences (all)   | 3 / 131 (2.29%)<br>3<br><br>0 / 131 (0.00%)<br>0                             |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)  | 4 / 131 (3.05%)<br>4   |  |  |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)<br><br>Confusional state<br>subjects affected / exposed<br>occurrences (all)<br><br>Depression<br>subjects affected / exposed<br>occurrences (all) | 0 / 131 (0.00%)<br>0<br><br>0 / 131 (0.00%)<br>0<br><br>0 / 131 (0.00%)<br>0 |  |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Back pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 131 (0.00%)<br>0<br><br>8 / 131 (6.11%)<br>9                             |  |  |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Upper respiratory tract infection   | 6 / 131 (4.58%)<br>6   |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 8 / 131 (6.11%) |  |  |
| occurrences (all)           | 8               |  |  |
| Urinary tract infection     |                 |  |  |
| subjects affected / exposed | 0 / 131 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 21 July 2016      | (1) To allow participants who suspend dosing after a first observance of ARIA to (a) restart at the same dose (rather than the next lower dose per Version 1) after ARIA resolution and (b) titrate up to the originally assigned dose (rather than continue on the next lower dose for the duration of the study). (2) Removed requirement to permanently discontinue treatment after severe symptomatic ARIA or serious ARIA (other medically important" criteria only); instead, in such participants, dosing could be suspended and then resumed at the same dose after ARIA and symptoms resolved or stabilized. (3) Regarding the management of recurrent ARIA, the amendment (a) allowed participants who had suspended dosing after a second episode to restart dosing, after ARIA resolution, at the next lower dose and continue uptitration (rather than remaining on the restart dose as in Version 1) and (b) required treatment discontinuation after 3 ARIA episodes (rather than requiring a third dose reduction with Sponsor approval). |
| 24 March 2017     | To allow apolipoprotein E (ApoE) ε4 carrier subjects randomised to high-dose aducanumab to receive the same high-dose aducanumab regimen already received by ApoE ε4 non-carriers (i.e., per this amendment, the high dose for carriers was changed from 6 to 10 mg/kg, which was also the high dose for noncarriers).  |
| 18 September 2017 | (1) Modified the percentage of primary endpoint data estimated to be available at the time of a potential blinded sample size re-estimation. (2) Provided additional details on the planned sample size re-estimation (including the maximum potential sample size). (3) Added information on an additional concentration and formulation for aducanumab used in the study.   |
| 28 June 2018      | (1) To reflect the agreement of the DMC that the characteristics or outcomes of the first event and recurrent events of ARIA were similar, the management of recurrent ARIA was modified so that a third episode of ARIA that requires dose suspension will no longer require study treatment discontinuation, and after recurrent ARIA resolves or stabilizes, dosing will resume at the same dose. (2) To extend the study such that participants nearing study completion under Protocol Version 5 can continue in the study and receive treatment until either the participant's EOT Visit at Week 338 (an additional 3 years of treatment) or until the last participant has had his or her Week 182 Visit, whichever occurred first. (3) To adjust the sample size from 450 to 535 participants per treatment group following the blinded sample size re-estimation to ensure adequate power to detect a mean treatment effect of 0.5 for the primary endpoint, as prespecified in Protocol Version 1.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

The study was halted prematurely based on a prespecified futility analysis and not based on safety concerns. Subjects discontinued due to study termination are included in "Reason not Specified" category in subject disposition tables above.

Notes:



