



## Clinical trial results:

### A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Intravenously Administered BIIB092 in Participants with Progressive Supranuclear Palsy

#### Summary

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2016-002554-21       |
| Trial protocol           | GB DE AT ES GR FR IT |
| Global end of trial date | 07 February 2020     |

#### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v1                |
| This version publication date  | 24 September 2020 |
| First version publication date | 24 September 2020 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 251PP301 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |                                 |
|------------------------------------|---------------------------------|
| ISRCTN number                      | -                               |
| ClinicalTrials.gov id (NCT number) | NCT03068468                     |
| WHO universal trial number (UTN)   | -                               |
| Other trial identifiers            | Bristol-Myers Squibb: CN002-012 |

Notes:

##### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Biogen  |
| Sponsor organisation address | 250 Binney Street, Cambridge, United States, 02142                  |
| Public contact               | Biogen Study Medical Director, Biogen,<br>clinicaltrials@biogen.com |
| Scientific contact           | Biogen Study Medical Director, Biogen,<br>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                       | 07 February 2020 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 07 February 2020 |
| Was the trial ended prematurely?                     | Yes              |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of BIIB092, compared to placebo, as measured by a change from baseline in the PSP Rating Scale (PSPRS) at Week 52 and to assess the safety and tolerability of BIIB092, relative to placebo, by measuring the frequency of deaths, SAEs, and AEs leading to discontinuation, and Grade 3 & 4 laboratory abnormalities.

Protection of trial subjects:

Written informed consent was obtained from each subject or subject's legally authorized representative (e.g., parent or 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                          | 01 June 2017 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | United States: 129     |
| Country: Number of subjects enrolled | Germany: 81            |
| Country: Number of subjects enrolled | Spain: 65              |
| Country: Number of subjects enrolled | France: 64             |
| Country: Number of subjects enrolled | Japan: 39              |
| Country: Number of subjects enrolled | United Kingdom: 26     |
| Country: Number of subjects enrolled | Italy: 25              |
| Country: Number of subjects enrolled | Canada: 16             |
| Country: Number of subjects enrolled | Russian Federation: 16 |
| Country: Number of subjects enrolled | Austria: 13            |
| Country: Number of subjects enrolled | Korea, Republic of: 8  |
| Country: Number of subjects enrolled | Greece: 7              |
| Country: Number of subjects enrolled | Australia: 1           |
| Worldwide total number of subjects   | 490                    |
| EEA total number of subjects         | 281                    |

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)                      | 119 |
| From 65 to 84 years                       | 371 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Subjects were enrolled at 89 investigative sites in the United States, Australia, Austria, Canada, France, Germany, Greece, Italy, Japan, Republic of Korea, Russia Federation, Spain and United Kingdom from June 01, 2017 to February 07, 2020.

### Pre-assignment

Screening details:

A total of 490 subjects were enrolled in the study and out of that 486 were treated. The study had two periods, Placebo-controlled (PC) and open-label extension (OLE) period.

### 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, Assessor |

### Arms

|                              |                    |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes                |
| <b>Arm title</b>             | BIIB092 Late Start |

Arm description:

Subjects assigned to BIIB092 matching placebo intravenous (IV) infusion once every 4 weeks for 48 weeks in double blind treatment period followed by BIIB092 50 milligrams per millilitre (mg/mL) IV infusion once every 4 weeks starting at Week 52 in the OLE period.

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

Dosage and administration details:

Subjects assigned to BIIB092 matching placebo IV infusion once every 4 weeks for 48 weeks.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | BIIB092               |
| Investigational medicinal product code | BIIB092               |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Subjects assigned to BIIB092 50 mg/mL IV infusion once every 4 weeks starting at Week 52.

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | BIIB092 Early Start |
|------------------|---------------------|

Arm description:

Subjects assigned to BIIB092 50 mg/mL IV infusion once every 4 weeks for 48 weeks in double blind treatment period followed by BIIB092 50 mg/mL IV infusion once every 4 weeks starting at Week 52 in the OLE period.

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | BIIB092               |
| Investigational medicinal product code | BIIB092               |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

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**Dosage and administration details:**

Subjects assigned to BIIB092 50 mg/mL IV infusion once every 4 weeks for 48 weeks in double blind treatment period followed by BIIB092 50 mg/mL IV infusion once every 4 weeks starting at Week 52 in the OLE period.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | BIIB092 Late Start | BIIB092 Early Start |
|---|--------------------|---------------------|
| Started   | 165                | 321                 |
| Completed   | 144                | 279                 |
| Not completed                                       | 21                 | 42                  |
| Consent withdrawn by subject                        | 3                  | 11                  |
| Adverse Event                                       | 16                 | 21                  |
| Death   | -                  | 1                   |
| Withdrawal by Parent/Guardian                       | 1                  | 2                   |
| Reason not specified                                | 1                  | 6                   |
| Lack of efficacy                                    | -                  | 1                   |

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**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 who started the baseline period are the subjects who were treated in the study.

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**Period 2**

|                              |                             |
|------------------------------|-----------------------------|
| Period 2 title               | Open-Label Extension Period |
| Is this the baseline period? | No                          |
| Allocation method            | Not applicable              |
| Blinding used                | Not blinded                 |

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**Arms**

|                              |                    |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes                |
| <b>Arm title</b>             | BIIB092 Late Start |

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**Arm description:**

Subjects assigned to BIIB092 matching placebo intravenous (IV) infusion once every 4 weeks for 48 weeks in double blind treatment period followed by BIIB092 50 milligrams per milliter (mg/mL) IV infusion once every 4 weeks starting at Week 52 in the OLE period.

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | BIIB092               |
| Investigational medicinal product code | BIIB092               |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

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**Dosage and administration details:**

Subjects assigned to BIIB092 50 mg/mL IV infusion once every 4 weeks starting at Week 52.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name   | Placebo               |
| Investigational medicinal product code   | BIIB092               |
| Other name   |                       |
| Pharmaceutical forms   | Solution for infusion |
| Routes of administration   | Intravenous use       |
| Dosage and administration details:   |                       |
| Subjects assigned to BIIB092 matching placebo IV infusion once every 4 weeks for 48 weeks. |                       |
| <b>Arm title</b>   | BIIB092 Early Start   |

Arm description:

Subjects assigned to BIIB092 50 mg/mL IV infusion once every 4 weeks for 48 weeks in double blind treatment period followed by BIIB092 50 mg/mL IV infusion once every 4 weeks starting at Week 52 in the OLE period.

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | BIIB092               |
| Investigational medicinal product code | BIIB092               |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Subjects assigned to BIIB092 50 mg/mL IV infusion once every 4 weeks for 48 weeks in double blind treatment period followed by BIIB092 50 mg/mL IV infusion once every 4 weeks starting at Week 52 in the OLE period.

| <b>Number of subjects in period 2<sup>[2]</sup></b> | BIIB092 Late Start | BIIB092 Early Start |
|---|--------------------|---------------------|
| Started   | 140                | 276                 |
| Completed   | 0                  | 0                   |
| Not completed                                       | 140                | 276                 |
| Consent withdrawn by subject                        | 7                  | 20                  |
| Failure to meet randomization criteria              | 2                  | -                   |
| Adverse Event                                       | 13                 | 17                  |
| Death   | -                  | 1                   |
| Withdrawal by Parent/Guardian                       | -                  | 4                   |
| Lost to follow-up                                   | 1                  | -                   |
| Reason not specified                                | 1                  | 4                   |
| Withdrawal by sponsor                               | 115                | 228                 |
| Lack of efficacy                                    | 1                  | 2                   |

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: The number of subjects starting the open-label extension period is not same as the number of subjects who completed the placebo controlled period because few of the subjects did not enter the open-label extension period.

## Baseline characteristics

### Reporting groups

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | BIIB092 Late Start |
|-----------------------|--------------------|

Reporting group description:

Subjects assigned to BIIB092 matching placebo intravenous (IV) infusion once every 4 weeks for 48 weeks in double blind treatment period followed by BIIB092 50 milligrams per millilitre (mg/mL) IV infusion once every 4 weeks starting at Week 52 in the OLE period.

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | BIIB092 Early Start |
|-----------------------|---------------------|

Reporting group description:

Subjects assigned to BIIB092 50 mg/mL IV infusion once every 4 weeks for 48 weeks in double blind treatment period followed by BIIB092 50 mg/mL IV infusion once every 4 weeks starting at Week 52 in the OLE period.

| Reporting group values             | BIIB092 Late Start | BIIB092 Early Start | Total |
|------------------------------------|--------------------|---------------------|-------|
| Number of subjects                 | 165                | 321                 | 486   |
| Age categorical<br>Units: Subjects |                    |                     |       |

|   |                |                |     |
|---|----------------|----------------|-----|
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 68.9<br>± 6.57 | 68.7<br>± 7.02 | -   |
| Sex: Female, Male<br>Units: subjects                                    |                |                |     |
| Female  | 74             | 136            | 210 |
| Male  | 91             | 185            | 276 |
| Race<br>Units: Subjects   |                |                |     |
| White   | 138            | 281            | 419 |
| Black or African American   | 1              | 1              | 2   |
| Asian Indian  | 3              | 3              | 6   |
| Chinese   | 0              | 1              | 1   |
| Japanese  | 16             | 23             | 39  |
| Asian Other   | 4              | 10             | 14  |
| Unknown   | 3              | 2              | 5   |
| Ethnicity<br>Units: Subjects  |                |                |     |
| Hispanic or Latino  | 5              | 7              | 12  |
| Not Hispanic or Latino  | 117            | 242            | 359 |
| Unknown or Not Reported   | 43             | 72             | 115 |

## End points

### End points reporting groups

|   |                     |
|---|---------------------|
| Reporting group title   | BIIB092 Late Start  |
| Reporting group description:<br>Subjects assigned to BIIB092 matching placebo intravenous (IV) infusion once every 4 weeks for 48 weeks in double blind treatment period followed by BIIB092 50 milligrams per millilitre (mg/mL) IV infusion once every 4 weeks starting at Week 52 in the OLE period. |                     |
| Reporting group title   | BIIB092 Early Start |
| Reporting group description:<br>Subjects assigned to BIIB092 50 mg/mL IV infusion once every 4 weeks for 48 weeks in double blind treatment period followed by BIIB092 50 mg/mL IV infusion once every 4 weeks starting at Week 52 in the OLE period.   |                     |
| Reporting group title   | BIIB092 Late Start  |
| Reporting group description:<br>Subjects assigned to BIIB092 matching placebo intravenous (IV) infusion once every 4 weeks for 48 weeks in double blind treatment period followed by BIIB092 50 milligrams per millilitre (mg/mL) IV infusion once every 4 weeks starting at Week 52 in the OLE period. |                     |
| Reporting group title   | BIIB092 Early Start |
| Reporting group description:<br>Subjects assigned to BIIB092 50 mg/mL IV infusion once every 4 weeks for 48 weeks in double blind treatment period followed by BIIB092 50 mg/mL IV infusion once every 4 weeks starting at Week 52 in the OLE period.   |                     |
| Subject analysis set title  | BIIB092 Late Start  |
| Subject analysis set type   | Safety analysis     |
| Subject analysis set description:<br>Subjects receiving at least one BIIB092 50 mg/mL IV infusion in the double blind treatment period, and if applicable, followed by BIIB092 50 mg/mL IV infusion once every 4 weeks starting at Week 52 in the open label extension period.                          |                     |
| Subject analysis set title  | BIIB092 Early Start |
| Subject analysis set type   | Safety analysis     |
| Subject analysis set description:<br>Subjects receiving at least one BIIB092 50 mg/mL IV infusion in the double blind treatment period, and if applicable, followed by BIIB092 50 mg/mL IV infusion once every 4 weeks starting at Week 52 in the open label extension period.                          |                     |

### Primary: Change From Baseline in Progressive Supranuclear Palsy Rating Scale (PSPRS) at Week 52

|  |  |
|--|--|
| End point title  | Change From Baseline in Progressive Supranuclear Palsy Rating Scale (PSPRS) at Week 52 |
| End point description:<br>The PSPRS is a quantitative measure of disability in participants with PSP. The PSPRS comprises 28 items in 6 areas. Six items are rated on a 3-point scale (0-2) and 22 are rated on a 5-point scale (0-4). The 6 areas are the History/Daily Activities, Mentation, Bulbar, Ocular Motor, Limb Motor, and Gait. The 28-item PSPRS total score ranges from 0 (normal) to 100. Fifteen items are selected to form a 15-item PSPRS and three domains are identified: Gait/Limb function, Ocular Motor, and Bulbar. The total 15-item PSPRS score ranges from 0 (normal) to 52. A positive change from baseline indicates worsening. Intent-to-Treat (ITT) population included randomized subjects who had received at least 1 dose of blinded study treatment (BIIB092 or Placebo). |  |
| End point type   | Primary  |
| End point timeframe:<br>Baseline, Week 52  |  |



| End point values                 | BIIB092 Late Start | BIIB092 Early Start |  |  |
|----------------------------------|--------------------|---------------------|--|--|
| Subject group type               | Reporting group    | Reporting group     |  |  |
| Number of subjects analysed      | 139 <sup>[1]</sup> | 278 <sup>[2]</sup>  |  |  |
| Units: Score on a scale          |                    |                     |  |  |
| arithmetic mean (standard error) |                    |                     |  |  |
| PSPRS: 28 items                  | 10.6 (± 0.8)       | 10.4 (± 0.6)        |  |  |
| PSPRS: 15 items                  | 7.57 (± 0.52)      | 7.29 (± 0.38)       |  |  |

Notes:

[1] - 'Number of Subjects Analyzed' signifies number of subjects who had response on Week 52.

[2] - 'Number of Subjects Analyzed' signifies number of subjects who had response on Week 52.

## Statistical analyses

| Statistical analysis title | 28-items |
|----------------------------|----------|
|----------------------------|----------|

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on a mixed model for repeated measures model (MMRM), with change from baseline in 28-item PSPRS total score as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline 28-item PSPRS, baseline 28-item PSPRS by time interaction, baseline Color Trails 2 test ( $\leq 170$  or  $> 170$  seconds) and region.

|   |  |
|---|--|
| Comparison groups                       | BIIB092 Late Start v BIIB092 Early Start |
| Number of subjects included in analysis | 417                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.8483                                 |
| Method                                  | Mixed model for repeated measures (MMRM) |
| Parameter estimate                      | Difference                               |
| Point estimate                          | -0.2                                     |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -2                                       |
| upper limit                             | 1.6                                      |

| Statistical analysis title | 15-items |
|----------------------------|----------|
|----------------------------|----------|

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in 15-item PSPRS total score as dependent variable and with fixed effects of treatment group, time (categorical), treatment group by-time interaction, baseline 15-item PSPRS, baseline 15-item PSPRS by time interaction, baseline Color Trails 2 test ( $\leq 170$  or  $> 170$  seconds) and region.

|   |  |
|---|--|
| Comparison groups                       | BIIB092 Late Start v BIIB092 Early Start |
| Number of subjects included in analysis | 417                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.6503                                 |
| Method                                  | MMRM                                     |
| Parameter estimate                      | Difference                               |
| Point estimate                          | -0.28                                    |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -1.5    |
| upper limit         | 0.94    |

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**Primary: Percentage of Subjects with Death, Serious Adverse Events (SAEs), Adverse Events (AEs) and Adverse Events (AEs) Leading to Discontinuation of Drug**

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|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects with Death, Serious Adverse Events (SAEs), Adverse Events (AEs) and Adverse Events (AEs) Leading to Discontinuation of Drug <sup>[3]</sup> |
|-----------------|---|

End point description:

AEs: any sign, symptom, or diagnosis/disease that is unfavorable or unintended, that is new, or if pre-existing, worsens in subjects administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. SAEs: an event that results in death; an event that, in the view of the investigator, places the subject at immediate risk of death (a life-threatening event); an outcome that results in a congenital anomaly/birth defect diagnosed in a child of a subject; an event that requires or prolongs inpatient hospitalization; an event that results in persistent or significant disability/incapacity. Safety population included all randomized subjects who had received at least one dose of study treatment (BII092 or Placebo).

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

End point timeframe:

up to 52 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistical analysis was planned to be reported for this endpoint.

| End point values                       | BII092 Late Start    | BII092 Early Start   |  |  |
|--|----------------------|----------------------|--|--|
| Subject group type                     | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed            | 162                  | 324                  |  |  |
| Units: Percentage of subjects          |                      |                      |  |  |
| number (not applicable)                |                      |                      |  |  |
| Death                                  | 4.9                  | 4.9                  |  |  |
| SAEs                                   | 32.1                 | 27.2                 |  |  |
| AEs                                    | 93.2                 | 92.9                 |  |  |
| AEs Leading to Discontinuation of Drug | 11.1                 | 7.4                  |  |  |

## Statistical analyses

No statistical analyses for this end point

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**Secondary: Change From Baseline in Movement Disorder Society (MDS)-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II at Week 52**

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|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Movement Disorder Society (MDS)-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II at Week 52 |
|-----------------|---|

End point description:

The MDS-UPDRS Part 2 includes 13 items assessing motor aspects of experiences of daily living (M-

EDL) these include speech, saliva and drooling, chewing and swallowing, handwriting, doing hobbies and other activities, eating tasks, tremor, dressing, hygiene, turning in bed, getting out of bed, walking and balance, and freezing. All items have 5 responses with uniform anchors of 0= normal, 1= slight, 2= mild, 3= moderate, and 4= severe. Total score ranges from 0 to 52, higher score indicating severe conditions. A positive change from baseline indicates worsening. ITT population included randomized subjects who had received at least 1 dose of blinded study treatment (BII092 or Placebo).

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 52    |           |

| End point values                 | BIIB092 Late Start | BIIB092 Early Start |  |  |
|----------------------------------|--------------------|---------------------|--|--|
| Subject group type               | Reporting group    | Reporting group     |  |  |
| Number of subjects analysed      | 143 <sup>[4]</sup> | 270 <sup>[5]</sup>  |  |  |
| Units: Score on a scale          |                    |                     |  |  |
| arithmetic mean (standard error) | 6.7 (± 0.6)        | 7.0 (± 0.4)         |  |  |

Notes:

[4] - 'Number of Subjects Analyzed' signifies the total number of subjects analyzed in this endpoint.

[5] - 'Number of Subjects Analyzed' signifies the total number of subjects analyzed in this endpoint.

## Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | BIIB092 Late Start vs BIIB092 Early Start |
|----------------------------|---|

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in MDS-UPDRS as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline MDS-UPDRS, baseline MDS-UPDRS by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region.

|   |  |
|---|--|
| Comparison groups                       | BIIB092 Late Start v BIIB092 Early Start |
| Number of subjects included in analysis | 413                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.6031                                 |
| Method                                  | MMRM                                     |
| Parameter estimate                      | Difference                               |
| Point estimate                          | 0.4                                      |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -1                                       |
| upper limit                             | 1.7                                      |

## Secondary: Clinical Global Impression of Change (CGI-C) Scale Score

|                 |  |
|-----------------|--|
| End point title | Clinical Global Impression of Change (CGI-C) Scale Score |
|-----------------|--|

End point description:

The CGI-C scale measures the change in the patient's clinical status from a specific point in time. Using a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse), with a score of 4 indicating no change. ITT population included randomized subjects who had received at least 1 dose of blinded study treatment (BII092 or Placebo).

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 52              |           |

| End point values                 | BIIB092 Late Start | BIIB092 Early Start |  |  |
|----------------------------------|--------------------|---------------------|--|--|
| Subject group type               | Reporting group    | Reporting group     |  |  |
| Number of subjects analysed      | 138 <sup>[6]</sup> | 271 <sup>[7]</sup>  |  |  |
| Units: Score on a scale          |                    |                     |  |  |
| arithmetic mean (standard error) | 5.3 (± 0.1)        | 5.2 (± 0.1)         |  |  |

Notes:

[6] - 'Number of Subjects Analyzed' signifies the total number of subjects analyzed in this endpoint.

[7] - 'Number of Subjects Analyzed' signifies the total number of subjects analyzed in this endpoint.

### Statistical analyses

| Statistical analysis title | BIIB092 Late Start vs BIIB092 Early Start |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with CGI-C as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline CGI-S, baseline CGI-S by time interaction, baseline Color Trails 2 test ( $\leq 170$  or  $> 170$  seconds) and region.

|   |  |
|---|--|
| Comparison groups                       | BIIB092 Late Start v BIIB092 Early Start |
| Number of subjects included in analysis | 409                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.7743                                 |
| Method                                  | MMRM                                     |
| Parameter estimate                      | Difference                               |
| Point estimate                          | 0  |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -0.2                                     |
| upper limit                             | 0.1                                      |

### Secondary: Change From Baseline in Progressive Supranuclear Palsy (PSP)-Cognitive Composite Battery Z-Score at Week 52

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Progressive Supranuclear Palsy (PSP)-Cognitive Composite Battery Z-Score at Week 52 |
|-----------------|---|

End point description:

The PSP cognitive composite battery is used to identify and characterize abnormal cognitive decline in PSP subjects. The PSP cognitive composite battery includes 13 sub-tests in total: 11 tests from the RBANS (only the picture naming is excluded), letter number sequencing test, and phonemic fluency test. Three domains are identified: Memory and learning, Visual-Motor function, and Working memory and Executive. A z-score transformation is applied for each component test at each visit, and the final total composite z-score is the average of the three domain z-scores. A negative change from baseline indicates worsening ITT population included randomized subjects who had received at least 1 dose of blinded study treatment (BIIB092 or Placebo).

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

End point timeframe:

Baseline, Week 52

| End point values                 | BIIB092 Late Start    | BIIB092 Early Start   |  |  |
|----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type               | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed      | 134 <sup>[8]</sup>    | 249 <sup>[9]</sup>    |  |  |
| Units: Score on a scale          |                       |                       |  |  |
| arithmetic mean (standard error) | -0.283 ( $\pm$ 0.032) | -0.245 ( $\pm$ 0.024) |  |  |

Notes:

[8] - 'Number of Subjects Analyzed' signifies the total number of subjects analyzed in this endpoint.

[9] - 'Number of Subjects Analyzed' signifies the total number of subjects analyzed in this endpoint.

## Statistical analyses

| Statistical analysis title | BIIB092 Late Start vs BIIB092 Early Start |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in PSP-cognitive composite battery as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline PSP-cognitive composite battery, baseline PSP-cognitive composite battery by time interaction, baseline Color Trails 2 test ( $\leq 170$  or  $>170$  seconds) and region.

|   |  |
|---|--|
| Comparison groups                       | BIIB092 Late Start v BIIB092 Early Start |
| Number of subjects included in analysis | 383                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.318                                  |
| Method                                  | MMRM                                     |
| Parameter estimate                      | Difference                               |
| Point estimate                          | 0.038                                    |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -0.036                                   |
| upper limit                             | 0.112                                    |

## Secondary: Change From Baseline in Repeatable Battery for the Assessment of Neuropsychological Disease Severity (RBANS) Scale at Week 52

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Repeatable Battery for the Assessment of Neuropsychological Disease Severity (RBANS) Scale at Week 52 |
|-----------------|---|

End point description:

The RBANS provides both a total scale score and scores for 5 different cognitive domains. Specifically, the test measures immediate memory, visuospatial/constructional ability, language, attention, and delayed memory. Scores from all subtests are aggregated into a total composite score. RBANS data were age-normed and analyzed as index scores (also referred to as standard scores), which have a mean of 100 and a standard deviation of 15. Higher scores on each sub measure and index indicate worsening. A negative change from baseline indicates better performance. ITT population included randomized subjects who had received at least 1 dose of blinded study treatment (BIIB092 or Placebo).

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

End point timeframe:

Baseline, Week 52

| End point values                 | BIIB092 Late Start  | BIIB092 Early Start |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 111 <sup>[10]</sup> | 222 <sup>[11]</sup> |  |  |
| Units: Score on a scale          |                     |                     |  |  |
| arithmetic mean (standard error) | -3.1 (± 0.7)        | -3.2 (± 0.5)        |  |  |

Notes:

[10] - 'Number of Subjects Analyzed' signifies the total number of subjects analyzed in this endpoint.

[11] - 'Number of Subjects Analyzed' signifies the total number of subjects analyzed in this endpoint.

## Statistical analyses

| Statistical analysis title | BIIB092 Late Start vs BIIB092 Early Start |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in RBANS as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline RBANS , baseline RBANS by time interaction, baseline Color Trails 2 test ( $\leq 170$  or  $> 170$  seconds and region).

|   |  |
|---|--|
| Comparison groups                       | BIIB092 Late Start v BIIB092 Early Start |
| Number of subjects included in analysis | 333                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.827                                  |
| Method                                  | MMRM                                     |
| Parameter estimate                      | Difference                               |
| Point estimate                          | -0.2                                     |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -1.8                                     |
| upper limit                             | 1.4                                      |

## Secondary: Change From Baseline in Progressive Supranuclear Palsy Quality of Life Scale (PSP-QoL) Score

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Progressive Supranuclear Palsy Quality of Life Scale (PSP-QoL) Score |
|-----------------|--|

End point description:

The PSP-QoL is a patient-reported outcome measure specifically for assessing the health-related quality of life in people living with PSP. It is validated 45-item questionnaire and visual analog scale (VAS) that is comprised of 2 subscales: physical health state (22 items), which covers mobility, dysarthria, dysphagia, visual disturbances, self-care and activities of daily living, and mental health state (23 items), which covers emotional, cognitive and social functioning. Items are given a 6-reponse option format (No Problem, Slight Problem, Moderate Problem, Marked Problem, Extreme Problem and Not Applicable). The subscale results are derived by summing the respective items for that subscale and transforming the scores into a range of 0 to 100, the higher the scores = greater impact of the disease. The PSP-QoL also comprises of a Life Satisfaction rating gauge, which is a VAS with a range of 0 (worst) to 100 (best). ITT population. Here, 'n' = number of subjects analyzed for each parameter.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 52    |           |

| End point values                             | BIIB092 Late Start  | BIIB092 Early Start |  |  |
|--|---------------------|---------------------|--|--|
| Subject group type                           | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed                  | 142 <sup>[12]</sup> | 264 <sup>[13]</sup> |  |  |
| Units: Score on a scale                      |                     |                     |  |  |
| arithmetic mean (standard error)             |                     |                     |  |  |
| Physical Scale Score (n=142, 264)            | 11.3 (± 1.5)        | 11.2 (± 1.1)        |  |  |
| Mental Scale Score (n=140, 264)              | 5.6 (± 1.4)         | 6.1 (± 1.0)         |  |  |
| Satisfaction With Your Life Today(n=141,264) | -3.7 (± 1.8)        | -5.4 (± 1.3)        |  |  |

Notes:

[12] - 'Number of Subjects Analyzed' signifies number of subjects who had response on Week 52.

[13] - 'Number of Subjects Analyzed' signifies number of subjects who had response on Week 52.

## Statistical analyses

| Statistical analysis title | BIIB092 Late Start vs BIIB092 Early Start |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Physical scale score: Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in PSP-QoL as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for PSP-QoL, baseline PSP-QoL by time interaction, baseline Color Trails 2 test ( $\leq 170$  or  $> 170$  seconds) and region.

|   |  |
|---|--|
| Comparison groups                       | BIIB092 Late Start v BIIB092 Early Start |
| Number of subjects included in analysis | 406                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.9304                                 |
| Method                                  | MMRM                                     |
| Parameter estimate                      | Difference                               |
| Point estimate                          | -0.2                                     |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -3.6                                     |
| upper limit                             | 3.3                                      |

| Statistical analysis title | BIIB092 Late Start vs BIIB092 Early Start |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Mental scale score: Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in PSPQoL as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-bytime interaction, baseline for PSP-QoL, baseline PSP-QoL by time interaction, baseline Color Trails 2 test ( $\leq 170$  or  $> 170$  seconds) and region.

|                   |  |
|-------------------|--|
| Comparison groups | BIIB092 Late Start v BIIB092 Early Start |
|-------------------|--|

|   |               |
|---|---------------|
| Number of subjects included in analysis | 406           |
| Analysis specification                  | Pre-specified |
| Analysis type                           | superiority   |
| P-value                                 | = 0.7859      |
| Method                                  | MMRM          |
| Parameter estimate                      | Difference    |
| Point estimate                          | 0.5           |
| Confidence interval                     |               |
| level                                   | 95 %          |
| sides                                   | 2-sided       |
| lower limit                             | -2.8          |
| upper limit                             | 3.7           |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | BIIB092 Late Start vs BIIB092 Early Start |
|-----------------------------------|---|

Statistical analysis description:

Satisfaction With Your Life Today: Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in PSPQoL as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-bytime interaction, baseline for PSP-QoL, baseline PSP-QoL by time interaction, baseline Color Trails 2 test ( $\leq 170$  or  $> 170$  seconds) and region.

|   |  |
|---|--|
| Comparison groups                       | BIIB092 Late Start v BIIB092 Early Start |
| Number of subjects included in analysis | 406                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.4297                                 |
| Method                                  | MMRM                                     |
| Parameter estimate                      | Difference                               |
| Point estimate                          | -1.7                                     |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -5.8                                     |
| upper limit                             | 2.5                                      |

## **Secondary: Change From Baseline in Schwab and England Activities of Daily Living (SEADL) Scale Score at Week 48**

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Schwab and England Activities of Daily Living (SEADL) Scale Score at Week 48 |
|-----------------|--|

End point description:

The SEADL scale is a means of assessing a person's ability to perform daily activities in terms of speed and independence, with 100% indicating total independence, falling to 0%, which indicates a state of complete dependence. The individual is asked to rate his or her function using an 11-point scale (10% increments), from 100% (completely independent; able to do all chores without slowness, difficulty, or impairment; essentially normal; unaware of any difficulty) to 0% (vegetative functions such as swallowing, bladder and bowels are not functioning; bedridden). A negative change from baseline indicates worsening. ITT population included randomized subjects who had received at least 1 dose of blinded study treatment (BIIB092 or Placebo).

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 48    |           |



| End point values                 | BIIB092 Late Start  | BIIB092 Early Start |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 140 <sup>[14]</sup> | 277 <sup>[15]</sup> |  |  |
| Units: Score on a scale          |                     |                     |  |  |
| arithmetic mean (standard error) | -13.7 (± 1.4)       | -11.7 (± 1.0)       |  |  |

Notes:

[14] - 'Number of Subjects Analyzed' signifies the total number of subjects analyzed in this endpoint.

[15] - 'Number of Subjects Analyzed' signifies the total number of subjects analyzed in this endpoint.

## Statistical analyses

| Statistical analysis title  | BIIB092 Late Start vs BIIB092 Early Start |
|---|---|
| Statistical analysis description:   |   |
| Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in SEADL as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for SEADL , baseline SEADL by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region. |   |
| Comparison groups   | BIIB092 Late Start v BIIB092 Early Start  |
| Number of subjects included in analysis   | 417                                       |
| Analysis specification  | Pre-specified                             |
| Analysis type   | superiority                               |
| P-value   | = 0.2084                                  |
| Method  | MMRM                                      |
| Parameter estimate  | Difference                                |
| Point estimate  | 2   |
| Confidence interval   |   |
| level   | 95 %                                      |
| sides   | 2-sided                                   |
| lower limit   | -1.1                                      |
| upper limit   | 5.2                                       |

## Secondary: Change From Baseline in Clinical Global Impression of Severity (CGI-S) Score at Week 52

| End point title  | Change From Baseline in Clinical Global Impression of Severity (CGI-S) Score at Week 52 |
|--|---|
| End point description:   |   |
| The Clinical Global Impression of Severity (CGI-S) Rating evaluates the severity of individual symptoms and treatment response in subjects with mental disorders. The CGI-S is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment. A rating of 1 is considered normal, or with the least severe symptoms, a rating of 7 is extremely ill, or the worst symptoms. ITT population included randomized subjects who had received at least 1 dose of blinded study treatment (BII092 or Placebo). |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Baseline, Week 52  |   |

| End point values                 | BIIB092 Late Start  | BIIB092 Early Start |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 140 <sup>[16]</sup> | 269 <sup>[17]</sup> |  |  |
| Units: Score on a scale          |                     |                     |  |  |
| arithmetic mean (standard error) | 0.6 (± 0.1)         | 0.6 (± 0.0)         |  |  |

Notes:

[16] - 'Number of Subjects Analyzed' signifies the total number of subjects analyzed in this endpoint.

[17] - 'Number of Subjects Analyzed' signifies the total number of subjects analyzed in this endpoint.

## Statistical analyses

| Statistical analysis title | BIIB092 Late Start vs BIIB092 Early Start |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in CGI-S as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for CGI-S, baseline CGI-S by time interaction, baseline Color Trails 2 test ( $\leq 170$  or  $> 170$  seconds) and region.

|   |  |
|---|--|
| Comparison groups                       | BIIB092 Late Start v BIIB092 Early Start |
| Number of subjects included in analysis | 409                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.5701                                 |
| Method                                  | MMRM                                     |
| Parameter estimate                      | Difference                               |
| Point estimate                          | 0  |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -0.2                                     |
| upper limit                             | 0.1                                      |

## Secondary: Change From Baseline in Phonemic Fluency Test Score at Week 48

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Phonemic Fluency Test Score at Week 48 |
|-----------------|--|

End point description:

Phonemic fluency is a sensitive test for assessing frontal lobe dysfunction. Participants are given a letter of the alphabet and asked to name as many words as they can that start with that letter in 1 minute. The score for each trial is auto-calculated as follows: Trial 1: Total number of correct responses for the first letter (range 1 to 40); Trial 2: Total number of correct responses for the second letter (range 1 to 40). More number of words correlates to better phonemic fluency. A negative change from baseline indicates worsening. ITT population included randomized subjects who had received at least 1 dose of blinded study treatment (BII092 or Placebo).

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

End point timeframe:

Baseline, Week 48

| End point values                     | BIIB092 Late Start  | BIIB092 Early Start |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 141 <sup>[18]</sup> | 273 <sup>[19]</sup> |  |  |
| Units: Score on a scale              |                     |                     |  |  |
| arithmetic mean (standard deviation) | -0.9 (± 0.4)        | 0.0 (± 0.3)         |  |  |

Notes:

[18] - 'Number of Subjects Analyzed' signifies the total number of subjects analyzed in this endpoint.

[19] - 'Number of Subjects Analyzed' signifies the total number of subjects analyzed in this endpoint.

## Statistical analyses

| Statistical analysis title  | BIIB092(Late Start Vs Early Start)       |
|---|--|
| Statistical analysis description:   |  |
| Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in Phonemic Fluency Test as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline Phonemic Fluency Test, baseline Phonemic Fluency Test by time interaction, baseline Color Trails 2 test ( $\leq 170$ or $> 170$ seconds) and region. |  |
| Comparison groups   | BIIB092 Late Start v BIIB092 Early Start |
| Number of subjects included in analysis   | 414                                      |
| Analysis specification  | Pre-specified                            |
| Analysis type   | superiority                              |
| P-value   | = 0.0517                                 |
| Method  | MMRM                                     |
| Confidence interval   |  |
| level   | 95 %                                     |
| sides   | 2-sided                                  |
| lower limit   | 0  |
| upper limit   | 1.8                                      |

## Secondary: Change From Baseline in Letter-Number Sequencing Test at Week 48

| End point title   | Change From Baseline in Letter-Number Sequencing Test at Week 48 |
|---|--|
| End point description:  |  |
| Letter number is a test of working memory which involves ordering a series of up to 8 letters and numbers in which the numbers are repeated back first in order starting with the lowest number, then followed by the letters in alphabetical order. Higher number of correct items is best and a negative change from baseline indicates worsening. ITT population included randomized subjects who had received at least 1 dose of blinded study treatment (BII092 or Placebo). |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Baseline, Week 48   |  |

| End point values                 | BIIB092 Late Start  | BIIB092 Early Start |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 139 <sup>[20]</sup> | 271 <sup>[21]</sup> |  |  |
| Units: Score on a scale          |                     |                     |  |  |
| arithmetic mean (standard error) | -1.9 (± 0.4)        | -1.1 (± 0.3)        |  |  |

Notes:

[20] - 'Number of Subjects Analyzed' signifies the total number of subjects analyzed in this endpoint.

[21] - 'Number of Subjects Analyzed' signifies the total number of subjects analyzed in this endpoint.

## Statistical analyses

| Statistical analysis title   | BIIB092 Late Start vs BIIB092 Early Start |
|--|---|
| Statistical analysis description:  |   |
| Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in Letter Number Sequence as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline Letter Number Sequence, baseline Letter Number Sequence by time interaction, baseline Color Trails 2 test ( $\leq 170$ or $> 170$ seconds) and region. |   |
| Comparison groups  | BIIB092 Late Start v BIIB092 Early Start  |
| Number of subjects included in analysis  | 410                                       |
| Analysis specification   | Pre-specified                             |
| Analysis type  | superiority                               |
| P-value  | = 0.0387                                  |
| Method   | MMRM                                      |
| Parameter estimate   | Difference                                |
| Point estimate   | 0.9                                       |
| Confidence interval  |   |
| level  | 95 %                                      |
| sides  | 2-sided                                   |
| lower limit  | 0   |
| upper limit  | 1.7                                       |

## Secondary: Change From Baseline in Color Trails at Week 48

| End point title   | Change From Baseline in Color Trails at Week 48 |
|---|---|
| End point description:  |   |
| The Color Trails test is a language free version of the Trail Making Test and was developed to allow for broader cross-cultural assessment. For Part 1 (color trails test 1), the respondent uses a pencil to rapidly connect circles numbered 1-25 in sequence. For Part 2 (color trails test 2), the respondent rapidly connects number circles in sequence, but alternates between pink and yellow background. The length of time to complete each trial is recorded, along with qualitative features of performance indicative of brain dysfunction, such as near-misses, prompts, number sequence errors, and color sequence errors. Less time indicates better performance. A positive change from baseline indicates worsening. ITT population included randomized subjects who had received at least 1 dose of blinded study treatment (BII092 or Placebo). |   |
| End point type  | Secondary                                       |
| End point timeframe:  |   |
| Baseline, Week 48   |   |

| End point values                 | BIIB092 Late Start  | BIIB092 Early Start |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 143 <sup>[22]</sup> | 279 <sup>[23]</sup> |  |  |
| Units: Seconds                   |                     |                     |  |  |
| arithmetic mean (standard error) |                     |                     |  |  |
| Color Trails Test 1              | 16.8 (± 3.6)        | 16.9 (± 2.7)        |  |  |
| Color Trails Test 2              | 10.6 (± 2.4)        | 10.5 (± 1.8)        |  |  |

Notes:

[22] - 'Number of Subjects Analyzed' signifies the total number of subjects analyzed in this endpoint.

[23] - 'Number of Subjects Analyzed' signifies the total number of subjects analyzed in this endpoint.

## Statistical analyses

| Statistical analysis title | BIIB092 Late Start vs BIIB092 Early Start |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Color Trails Test 1: Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in Color trails Test 1 as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for Color Trails Test 1, baseline Color Trails Test 1 by time interaction, baseline Color Trails 2 test ( $\leq 170$  or  $> 170$  seconds) and region.

|   |  |
|---|--|
| Comparison groups                       | BIIB092 Late Start v BIIB092 Early Start |
| Number of subjects included in analysis | 422                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.9815                                 |
| Method                                  | MMRM                                     |
| Parameter estimate                      | Difference                               |
| Point estimate                          | 0.1                                      |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -8.1                                     |
| upper limit                             | 8.3                                      |

| Statistical analysis title | BIIB092 Late Start vs BIIB092 Early Start |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Color Trails Test 2: Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in Color Trails Test 2 as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for Color Trails Test 2, baseline Color Trails Test 2 by time interaction, and region.

|   |  |
|---|--|
| Comparison groups                       | BIIB092 Late Start v BIIB092 Early Start |
| Number of subjects included in analysis | 422                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.9869                                 |
| Method                                  | MMRM                                     |
| Parameter estimate                      | Difference                               |
| Point estimate                          | 0  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -5.7    |
| upper limit         | 5.6     |

## Secondary: Change From Baseline in Montreal Cognitive Assessment (MoCA) Score at Week 48

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Montreal Cognitive Assessment (MoCA) Score at Week 48 |
|-----------------|---|

End point description:

The MOCA was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive function, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Scores on the MOCA range from 0-30, with higher score being better performance. A negative change from baseline indicates worsening. ITT population included randomized subjects who had received at least 1 dose of blinded study treatment (BII092 or Placebo).

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

End point timeframe:

Baseline, Week 48

| End point values                 | BIIB092 Late Start  | BIIB092 Early Start |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 136 <sup>[24]</sup> | 264 <sup>[25]</sup> |  |  |
| Units: Score on a scale          |                     |                     |  |  |
| arithmetic mean (standard error) | -1.0 (± 0.3)        | -0.5 (± 0.2)        |  |  |

Notes:

[24] - 'Number of Subjects Analyzed' signifies the total number of subjects analyzed in this endpoint.

[25] - 'Number of Subjects Analyzed' signifies the total number of subjects analyzed in this endpoint.

## Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | BIIB092 Late Start vs BIIB092 Early Start |
|----------------------------|---|

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in MoCA as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for MoCA, baseline MoCA by time interaction, baseline Color Trails 2 test ( $\leq 170$  or  $> 170$  seconds) and region.

|   |  |
|---|--|
| Comparison groups                       | BIIB092 Late Start v BIIB092 Early Start |
| Number of subjects included in analysis | 400                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.1763                                 |
| Method                                  | MMRM                                     |
| Parameter estimate                      | Difference                               |
| Point estimate                          | 0.5                                      |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -0.2    |
| upper limit         | 1.2     |

### Secondary: Number of Participants with Treatment Emergent Antibodies (anti-BIIB092) Positive Results in Serum

|   |  |
|---|--|
| End point title   | Number of Participants with Treatment Emergent Antibodies (anti-BIIB092) Positive Results in Serum |
| End point description:<br>ADA population – subset of the safety population with at least one evaluable post-baseline evaluable ADA samples. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Up to Week 48   |  |

| End point values            | BIIB092 Late Start   | BIIB092 Early Start  |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 160 <sup>[26]</sup>  | 323 <sup>[27]</sup>  |  |  |
| Units: Subjects             | 7                    | 0                    |  |  |

Notes:

[26] - 'Number of Subjects Analyzed' signifies the total number of subjects analyzed in this endpoint

[27] - 'Number of Subjects Analyzed' signifies the total number of subjects analyzed in this endpoint

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline of Brain Volumes as Determined by MRI at Week 52

|  |   |
|--|---|
| End point title  | Change From Baseline of Brain Volumes as Determined by MRI at Week 52 |
| End point description:<br>A 3 dimension (3D) T1-weighted MRI was performed to estimate brain volumes (e.g., ventricles, whole brain, midbrain, pons, superior cerebellar peduncle, third ventricle, and frontal lobes). Efficacy MRI population is the subset of the ITT population who had a least one measurable brain volumetric measurement. Here, 'n' signifies the number of subjects analyzed for each parameter. |   |
| End point type   | Secondary   |
| End point timeframe:<br>Baseline, Week 52  |   |

| End point values                                   | BIIB092 Late Start  | BIIB092 Early Start |  |  |
|--|---------------------|---------------------|--|--|
| Subject group type                                 | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed                        | 114 <sup>[28]</sup> | 238 <sup>[29]</sup> |  |  |
| Units: Cubic centimeter (cm <sup>3</sup> )         |                     |                     |  |  |
| arithmetic mean (standard error)                   |                     |                     |  |  |
| Ventricles Volume: Change at Week 52 (n =103,222)  | 3.823 (± 0.302)     | 3.802 (± 0.216)     |  |  |
| Whole Brain Volume: Change at Week 52(n =101,210)  | -18.612 (± 1.296)   | -19.126 (± 0.950)   |  |  |
| Midbrain Volume: Change at Week 52 (n =108, 224)   | -0.116 (± 0.008)    | -0.120 (± 0.006)    |  |  |
| Pons Volume: Change at Week 52 (n =100, 223)       | -0.198 (± 0.017)    | -0.198 (± 0.012)    |  |  |
| Cerebellar Peduncle Volume:ChangeWeek52(n=101,216) | -0.005 (± 0.002)    | -0.004 (± 0.002)    |  |  |
| Third Ventricle Volume:Change at Week52(n=114,238) | 0.140 (± 0.014)     | 0.146 (± 0.010)     |  |  |
| Frontal Lobe Volume: Change at Week 52 (n =89,178) | 1.184 (± 0.279)     | 1.143 (± 0.205)     |  |  |

Notes:

[28] - 'Number of Subjects Analyzed' signifies number of subjects who had response on Week 52.

[29] - 'Number of Subjects Analyzed' signifies number of subjects who had response on Week 52.

## Statistical analyses

| Statistical analysis title  | Ventricles Volume                        |
|---|--|
| Statistical analysis description:   |  |
| Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in MRI region as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for MRI region, baseline MRI region by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region. |  |
| Comparison groups   | BIIB092 Late Start v BIIB092 Early Start |
| Number of subjects included in analysis   | 352                                      |
| Analysis specification  | Pre-specified                            |
| Analysis type   | superiority                              |
| P-value   | = 0.9527                                 |
| Method  | MMRM                                     |
| Parameter estimate  | Difference                               |
| Point estimate  | -0.021                                   |
| Confidence interval   |  |
| level   | 95 %                                     |
| sides   | 2-sided                                  |
| lower limit   | -0.726                                   |
| upper limit   | 0.684                                    |

| Statistical analysis title  | Whole Brain Volume |
|---|--------------------|
| Statistical analysis description:   |                    |
| Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in MRI region as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for MRI region, baseline MRI region by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region. |                    |



|   |  |
|---|--|
| Comparison groups                       | BIIB092 Late Start v BIIB092 Early Start |
| Number of subjects included in analysis | 352                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.7357                                 |
| Method                                  | MMRM                                     |
| Parameter estimate                      | Difference                               |
| Point estimate                          | -0.514                                   |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -3.506                                   |
| upper limit                             | 2.478                                    |

|                                   |                 |
|-----------------------------------|-----------------|
| <b>Statistical analysis title</b> | Midbrain Volume |
|-----------------------------------|-----------------|

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in MRI region as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for MRI region, baseline MRI region by time interaction, baseline Color Trails 2 test ( $\leq 170$  or  $> 170$  seconds) and region.

|   |  |
|---|--|
| Comparison groups                       | BIIB092 Late Start v BIIB092 Early Start |
| Number of subjects included in analysis | 352                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.6439                                 |
| Method                                  | MMRM                                     |
| Parameter estimate                      | Difference                               |
| Point estimate                          | -0.004                                   |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -0.023                                   |
| upper limit                             | 0.014                                    |

|                                   |             |
|-----------------------------------|-------------|
| <b>Statistical analysis title</b> | Pons Volume |
|-----------------------------------|-------------|

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in MRI region as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for MRI region, baseline MRI region by time interaction, baseline Color Trails 2 test ( $\leq 170$  or  $> 170$  seconds) and region.

|                   |  |
|-------------------|--|
| Comparison groups | BIIB092 Late Start v BIIB092 Early Start |
|-------------------|--|

|   |               |
|---|---------------|
| Number of subjects included in analysis | 352           |
| Analysis specification                  | Pre-specified |
| Analysis type                           | superiority   |
| P-value                                 | = 0.9864      |
| Method                                  | MMRM          |
| Parameter estimate                      | Difference    |
| Point estimate                          | 0             |
| Confidence interval                     |               |
| level                                   | 95 %          |
| sides                                   | 2-sided       |
| lower limit                             | -0.039        |
| upper limit                             | 0.04          |

|                                   |                            |
|-----------------------------------|----------------------------|
| <b>Statistical analysis title</b> | Cerebellar Peduncle Volume |
|-----------------------------------|----------------------------|

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in MRI region as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for MRI region, baseline MRI region by time interaction, baseline Color Trails 2 test ( $\leq 170$  or  $> 170$  seconds) and region.

|   |  |
|---|--|
| Comparison groups                       | BIIB092 Late Start v BIIB092 Early Start |
| Number of subjects included in analysis | 352                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.7529                                 |
| Method                                  | MMRM                                     |
| Parameter estimate                      | Difference                               |
| Point estimate                          | 0.001                                    |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -0.004                                   |
| upper limit                             | 0.006                                    |

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Third Ventricle Volume |
|-----------------------------------|------------------------|

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in MRI region as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for MRI region, baseline MRI region by time interaction, baseline Color Trails 2 test ( $\leq 170$  or  $> 170$  seconds) and region.

|   |  |
|---|--|
| Comparison groups                       | BIIB092 Late Start v BIIB092 Early Start |
| Number of subjects included in analysis | 352                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.685                                  |
| Method                                  | MMRM                                     |
| Parameter estimate                      | Difference                               |
| Point estimate                          | 0.006                                    |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -0.025  |
| upper limit         | 0.038   |

|                                   |                     |
|-----------------------------------|---------------------|
| <b>Statistical analysis title</b> | Frontal Lobe Volume |
|-----------------------------------|---------------------|

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in MRI region as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for MRI region, baseline MRI region by time interaction, baseline Color Trails 2 test ( $\leq 170$  or  $> 170$  seconds) and region.

|   |  |
|---|--|
| Comparison groups                       | BIIB092 Late Start v BIIB092 Early Start |
| Number of subjects included in analysis | 352                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.9                                    |
| Method                                  | MMRM                                     |
| Parameter estimate                      | Difference                               |
| Point estimate                          | -0.041                                   |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -0.68                                    |
| upper limit                             | 0.598                                    |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

up to 140 weeks

Adverse event reporting additional description:

Safety population included all randomized subjects who had received at least one dose of study treatment (BII092 or Placebo).

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

### Reporting groups

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | BII092 Early Start |
|-----------------------|--------------------|

Reporting group description:

Subjects receiving at least one BII092 50 mg/mL IV infusion in the double blind treatment period, and if applicable, followed by BII092 50 mg/mL IV infusion once every 4 weeks starting at Week 52 in the open label extension period.

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | BII092 Late Start |
|-----------------------|-------------------|

Reporting group description:

Subjects receiving at least one BII092 50 mg/mL IV infusion in the double-blind treatment period, and if applicable, followed by BII092 50 mg/mL IV infusion once every 4 weeks starting at Week 52 in the open label extension period.

| Serious adverse events  | BII092 Early Start | BII092 Late Start |  |
|---|--------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                    |                   |  |
| subjects affected / exposed   | 129 / 324 (39.81%) | 82 / 162 (50.62%) |  |
| number of deaths (all causes)                                       | 32                 | 18                |  |
| number of deaths resulting from adverse events                      |                    |                   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                   |  |
| Breast cancer   |                    |                   |  |
| subjects affected / exposed   | 0 / 324 (0.00%)    | 1 / 162 (0.62%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0              | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0             |  |
| Breast neoplasm   |                    |                   |  |
| subjects affected / exposed   | 0 / 324 (0.00%)    | 1 / 162 (0.62%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0              | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0             |  |
| Colorectal cancer   |                    |                   |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung adenocarcinoma                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malignant melanoma                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malignant melanoma in situ                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastatic gastric cancer                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatic carcinoma                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Pituitary tumour benign                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Prostate cancer                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Aortic aneurysm                                 |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Deep vein thrombosis                                 |                 |                 |  |
| subjects affected / exposed                          | 2 / 324 (0.62%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Haematoma  |                 |                 |  |
| subjects affected / exposed                          | 1 / 324 (0.31%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Orthostatic hypotension                              |                 |                 |  |
| subjects affected / exposed                          | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Cyst   |                 |                 |  |
| subjects affected / exposed                          | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Death  |                 |                 |  |
| subjects affected / exposed                          | 4 / 324 (1.23%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all      | 0 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 4           | 0 / 1           |  |
| Drowning   |                 |                 |  |
| subjects affected / exposed                          | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Euthanasia   |                 |                 |  |
| subjects affected / exposed                          | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           |  |
| Gait disturbance                                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 324 (0.62%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gait inability                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| General physical health deterioration           |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Multiple organ dysfunction syndrome             |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Systemic inflammatory response syndrome         |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders        |                 |                 |  |
| Acquired phimosis                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Benign prostatic hyperplasia                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Prostatitis                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 324 (0.62%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal           |                 |                 |  |

|   |                  |                  |  |  |
|---|------------------|------------------|--|--|
| disorders                                       |                  |                  |  |  |
| Acute respiratory failure                       |                  |                  |  |  |
| subjects affected / exposed                     | 6 / 324 (1.85%)  | 1 / 162 (0.62%)  |  |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |  |
| Aspiration                                      |                  |                  |  |  |
| subjects affected / exposed                     | 1 / 324 (0.31%)  | 3 / 162 (1.85%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |  |
| Choking   |                  |                  |  |  |
| subjects affected / exposed                     | 0 / 324 (0.00%)  | 2 / 162 (1.23%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |  |
| Chronic obstructive pulmonary disease           |                  |                  |  |  |
| subjects affected / exposed                     | 1 / 324 (0.31%)  | 2 / 162 (1.23%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |  |
| Dyspnoea  |                  |                  |  |  |
| subjects affected / exposed                     | 2 / 324 (0.62%)  | 0 / 162 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |  |
| Pleural effusion                                |                  |                  |  |  |
| subjects affected / exposed                     | 0 / 324 (0.00%)  | 1 / 162 (0.62%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |  |
| Pneumonia aspiration                            |                  |                  |  |  |
| subjects affected / exposed                     | 18 / 324 (5.56%) | 12 / 162 (7.41%) |  |  |
| occurrences causally related to treatment / all | 0 / 19           | 0 / 15           |  |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 5            |  |  |
| Pneumothorax                                    |                  |                  |  |  |
| subjects affected / exposed                     | 0 / 324 (0.00%)  | 1 / 162 (0.62%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 3 / 324 (0.93%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| Pulmonary oedema                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory arrest                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory depression                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Respiratory distress                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 3 / 162 (1.85%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2           |  |
| Psychiatric disorders                           |                 |                 |  |
| Agitation                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anxiety   |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Assisted suicide                                |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Confusional state                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hallucination                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Insomnia  |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mental status changes                           |                 |                 |  |
| subjects affected / exposed                     | 2 / 324 (0.62%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Suicidal ideation                               |                 |                 |  |
| subjects affected / exposed                     | 3 / 324 (0.93%) | 2 / 162 (1.23%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Suicide attempt                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 324 (0.62%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Blood creatine phosphokinase increased          |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemoglobin decreased                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Liver function test increased                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lumbar puncture                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Ankle fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cervical vertebral fracture                     |                 |                 |  |
| subjects affected / exposed                     | 5 / 324 (1.54%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clavicle fracture                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Concussion                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Contusion                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Craniocerebral injury                           |                 |                 |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 324 (0.31%)   | 0 / 162 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Facial bones fracture                           |                   |                   |  |
| subjects affected / exposed                     | 0 / 324 (0.00%)   | 1 / 162 (0.62%)   |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Fall  |                   |                   |  |
| subjects affected / exposed                     | 49 / 324 (15.12%) | 17 / 162 (10.49%) |  |
| occurrences causally related to treatment / all | 0 / 56            | 0 / 19            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Femoral neck fracture                           |                   |                   |  |
| subjects affected / exposed                     | 3 / 324 (0.93%)   | 1 / 162 (0.62%)   |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Femur fracture                                  |                   |                   |  |
| subjects affected / exposed                     | 3 / 324 (0.93%)   | 0 / 162 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Fracture  |                   |                   |  |
| subjects affected / exposed                     | 0 / 324 (0.00%)   | 1 / 162 (0.62%)   |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hip fracture                                    |                   |                   |  |
| subjects affected / exposed                     | 2 / 324 (0.62%)   | 1 / 162 (0.62%)   |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Human bite                                      |                   |                   |  |
| subjects affected / exposed                     | 0 / 324 (0.00%)   | 1 / 162 (0.62%)   |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Humerus fracture                                |                   |                   |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 324 (0.62%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Joint dislocation                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lumbar vertebral fracture                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 2 / 162 (1.23%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal foreign body                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Open globe injury                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Periprosthetic fracture                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post procedural haemorrhage                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Radius fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 3 / 324 (0.93%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rib fracture                                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 4 / 324 (1.23%) | 3 / 162 (1.85%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Road traffic accident                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Scapula fracture                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin laceration                                 |                 |                 |  |
| subjects affected / exposed                     | 4 / 324 (1.23%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal compression fracture                     |                 |                 |  |
| subjects affected / exposed                     | 3 / 324 (0.93%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subdural haematoma                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 324 (0.62%) | 2 / 162 (1.23%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tendon injury                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tendon rupture                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thermal burn                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thoracic vertebral fracture                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tibia fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Traumatic haematoma                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Traumatic intracranial haemorrhage              |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wrist fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wrong dose                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Acute myocardial infarction                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 324 (0.00%) | 2 / 162 (1.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrioventricular block complete                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrioventricular block second degree            |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac arrest                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardio-respiratory arrest                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Hypertensive heart disease                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Myocardial ischaemia                            |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Nervous system disorders                        |                 |                 |  |
| Akathisia                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral disorder                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 3 / 324 (0.93%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyskinesia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Encephalopathy                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epilepsy  |                 |                 |  |
| subjects affected / exposed                     | 2 / 324 (0.62%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lumbosacral radiculopathy                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolic encephalopathy                        |                 |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 324 (0.31%)  | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Monoparesis                                     |                  |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%)  | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Movement disorder                               |                  |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%)  | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Neurological decompensation                     |                  |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%)  | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Noninfective encephalitis                       |                  |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%)  | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 1 / 1           |  |
| Peroneal nerve palsy                            |                  |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%)  | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Progressive supranuclear palsy                  |                  |                 |  |
| subjects affected / exposed                     | 10 / 324 (3.09%) | 8 / 162 (4.94%) |  |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 9           |  |
| deaths causally related to treatment / all      | 0 / 7            | 0 / 3           |  |
| Seizure   |                  |                 |  |
| subjects affected / exposed                     | 2 / 324 (0.62%)  | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Somnolence                                      |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Status epilepticus</b>                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Subarachnoid haemorrhage</b>                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Syncope</b>                                  |                 |                 |  |
| subjects affected / exposed                     | 3 / 324 (0.93%) | 2 / 162 (1.23%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Transient ischaemic attack</b>               |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 2 / 162 (1.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Blood and lymphatic system disorders</b>     |                 |                 |  |
| <b>Anaemia</b>                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Iron deficiency anaemia</b>                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 2 / 162 (1.23%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Gastrointestinal disorders</b>               |                 |                 |  |
| <b>Colitis microscopic</b>                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Constipation</b>                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 324 (0.31%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dysphagia                                       |                 |                 |  |
| subjects affected / exposed                     | 7 / 324 (2.16%) | 6 / 162 (3.70%) |  |
| occurrences causally related to treatment / all | 0 / 7           | 1 / 6           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Faecaloma                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Femoral hernia                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastritis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hernial eventration                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hiatus hernia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Large intestine polyp                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Melaena   |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Umbilical hernia                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper gastrointestinal haemorrhage              |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Volvulus  |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting  |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Cholelithiasis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Dermal cyst                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 3 / 324 (0.93%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Calculus urinary                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hydronephrosis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nephrolithiasis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal impairment                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ureterolithiasis                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urge incontinence                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary retention                               |                 |                 |  |
| subjects affected / exposed                     | 2 / 324 (0.62%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 324 (0.62%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chondrocalcinosis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematoma muscle                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Muscle rigidity                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteitis  |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteoarthritis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pain in extremity                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Abscess neck                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacteraemia                                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 324 (0.62%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Bacterial infection                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchitis                                      |                 |                 |  |
| subjects affected / exposed                     | 3 / 324 (0.93%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridium difficile colitis                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cystitis  |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulitis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia urinary tract infection             |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infection                                       |                 |                 |  |



|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 324 (0.00%)  | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Influenza                                       |                  |                 |  |
| subjects affected / exposed                     | 2 / 324 (0.62%)  | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Parainfluenzae virus infection                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%)  | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pneumonia                                       |                  |                 |  |
| subjects affected / exposed                     | 16 / 324 (4.94%) | 5 / 162 (3.09%) |  |
| occurrences causally related to treatment / all | 0 / 18           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 0           |  |
| Pneumonia influenzal                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%)  | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pulmonary sepsis                                |                  |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%)  | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Pulmonary tuberculosis                          |                  |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%)  | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1            | 0 / 0           |  |
| Respiratory syncytial virus bronchitis          |                  |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%)  | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Respiratory tract infection                     |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 324 (0.62%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis  |                 |                 |  |
| subjects affected / exposed                     | 4 / 324 (1.23%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Septic shock                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subcutaneous abscess                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 5 / 324 (1.54%) | 5 / 162 (3.09%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urosepsis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Viral infection                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound infection staphylococcal                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 324 (0.31%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Dehydration                                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 324 (0.62%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetes mellitus inadequate control            |                 |                 |  |
| subjects affected / exposed                     | 0 / 324 (0.00%) | 1 / 162 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Failure to thrive                               |                 |                 |  |
| subjects affected / exposed                     | 2 / 324 (0.62%) | 0 / 162 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | BIIB092 Early Start | BIIB092 Late Start |  |
|---|---------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                     |                    |  |
| subjects affected / exposed                           | 269 / 324 (83.02%)  | 143 / 162 (88.27%) |  |
| Investigations  |                     |                    |  |
| Weight decreased                                      |                     |                    |  |
| subjects affected / exposed                           | 23 / 324 (7.10%)    | 6 / 162 (3.70%)    |  |
| occurrences (all)                                     | 24                  | 6                  |  |
| Injury, poisoning and procedural complications        |                     |                    |  |
| Contusion   |                     |                    |  |
| subjects affected / exposed                           | 58 / 324 (17.90%)   | 31 / 162 (19.14%)  |  |
| occurrences (all)                                     | 96                  | 61                 |  |
| Head injury   |                     |                    |  |
| subjects affected / exposed                           | 27 / 324 (8.33%)    | 12 / 162 (7.41%)   |  |
| occurrences (all)                                     | 32                  | 15                 |  |
| Fall  |                     |                    |  |
| subjects affected / exposed                           | 194 / 324 (59.88%)  | 96 / 162 (59.26%)  |  |
| occurrences (all)                                     | 497                 | 295                |  |
| Skin abrasion   |                     |                    |  |
| subjects affected / exposed                           | 35 / 324 (10.80%)   | 13 / 162 (8.02%)   |  |
| occurrences (all)                                     | 64                  | 36                 |  |
| Rib fracture  |                     |                    |  |

|  |                         |                         |  |
|--|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 18 / 324 (5.56%)<br>20  | 12 / 162 (7.41%)<br>14  |  |
| Skin laceration<br>subjects affected / exposed<br>occurrences (all)  | 48 / 324 (14.81%)<br>68 | 24 / 162 (14.81%)<br>41 |  |
| Vascular disorders<br>Haematoma<br>subjects affected / exposed<br>occurrences (all)  | 30 / 324 (9.26%)<br>49  | 16 / 162 (9.88%)<br>26  |  |
| Hypertension<br>subjects affected / exposed<br>occurrences (all)   | 9 / 324 (2.78%)<br>12   | 10 / 162 (6.17%)<br>10  |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)  | 20 / 324 (6.17%)<br>24  | 13 / 162 (8.02%)<br>17  |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)   | 40 / 324 (12.35%)<br>68 | 23 / 162 (14.20%)<br>34 |  |
| General disorders and administration<br>site conditions<br>Oedema peripheral<br>subjects affected / exposed<br>occurrences (all) | 21 / 324 (6.48%)<br>27  | 5 / 162 (3.09%)<br>6    |  |
| Gastrointestinal disorders<br>Constipation<br>subjects affected / exposed<br>occurrences (all)                                   | 47 / 324 (14.51%)<br>57 | 18 / 162 (11.11%)<br>19 |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 30 / 324 (9.26%)<br>35  | 12 / 162 (7.41%)<br>17  |  |
| Dysphagia<br>subjects affected / exposed<br>occurrences (all)  | 22 / 324 (6.79%)<br>24  | 10 / 162 (6.17%)<br>10  |  |
| Respiratory, thoracic and mediastinal<br>disorders<br>Cough  |                         |                         |  |

|  |   |   |  |
|--|---|---|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>19 / 324 (5.86%)</p> <p>21</p> <p>10 / 324 (3.09%)</p> <p>11</p>   | <p>6 / 162 (3.70%)</p> <p>7</p> <p>9 / 162 (5.56%)</p> <p>9</p>   |  |
| <p>Skin and subcutaneous tissue disorders</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>18 / 324 (5.56%)</p> <p>20</p>   | <p>7 / 162 (4.32%)</p> <p>7</p>   |  |
| <p>Psychiatric disorders</p> <p>Depression</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Suicidal ideation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>17 / 324 (5.25%)</p> <p>18</p> <p>24 / 324 (7.41%)</p> <p>29</p> <p>19 / 324 (5.86%)</p> <p>21</p>                                   | <p>8 / 162 (4.94%)</p> <p>8</p> <p>18 / 162 (11.11%)</p> <p>18</p> <p>10 / 162 (6.17%)</p> <p>14</p>                              |  |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Musculoskeletal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain in extremity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>21 / 324 (6.48%)</p> <p>22</p> <p>24 / 324 (7.41%)</p> <p>27</p> <p>22 / 324 (6.79%)</p> <p>22</p> <p>21 / 324 (6.48%)</p> <p>22</p> | <p>7 / 162 (4.32%)</p> <p>9</p> <p>11 / 162 (6.79%)</p> <p>19</p> <p>8 / 162 (4.94%)</p> <p>9</p> <p>7 / 162 (4.32%)</p> <p>7</p> |  |
| <p>Infections and infestations</p> <p>Bronchitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>19 / 324 (5.86%)</p> <p>23</p>   | <p>8 / 162 (4.94%)</p> <p>11</p>  |  |

|                             |                   |                   |  |
|-----------------------------|-------------------|-------------------|--|
| Nasopharyngitis             |                   |                   |  |
| subjects affected / exposed | 36 / 324 (11.11%) | 17 / 162 (10.49%) |  |
| occurrences (all)           | 51                | 21                |  |
| Urinary tract infection     |                   |                   |  |
| subjects affected / exposed | 78 / 324 (24.07%) | 39 / 162 (24.07%) |  |
| occurrences (all)           | 125               | 62                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 25 August 2017    | Sponsor name from BMS to Biogen. This includes replacing the BMS title page with the Biogen title page, inserting the Biogen Sponsor Signature Page and Biogen Sponsor Information section, changing the compound name from BMS-986168 to BIIB092 throughout the document, and changing the study name from CN002012 to 251PP301.         |
| 13 September 2017 | Sponsor name changed from BMS to Biogen. This includes replacing the BMS title page with the Biogen title page, inserting the Biogen Sponsor Signature Page and Biogen Sponsor Information section, changing the compound name from BMS-986168 to BIIB092 throughout the document, and changing the study name from CN002012 to 251PP301. |
| 14 November 2017  | Missing safety assessment, 12-lead electrocardiogram (ECG), and instruction to the assess infusion site to the double-blind schedule of events was added.   |
| 16 May 2018       | Increase in the study sample size.  |
| 24 May 2018       | An error was corrected in the decision criteria that would allow a subject who no longer has an active hepatitis C infection to enroll in the study.  |
| 01 February 2019  | The study treatment product provided for use in the open-label extension period, to include the 2000 milligram per vial (mg/vial).  |

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.

Study got terminated as the primary endpoint was not met. PC period was completed at the time of termination. The study was not terminated due to a safety concern.

Notes: