



## Clinical trial results:

### A Multicenter, Open-Label, Long-Term Safety Extension of Phase II Studies ABE4869g and ABE4955g in Patients with Mild to Moderate Alzheimer's Disease

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2012-003242-33   |
| Trial protocol           | GB DE ES         |
| Global end of trial date | 08 February 2017 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 16 February 2018 |
| First version publication date | 16 February 2018 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | GN28525 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01723826 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                                     |
|------------------------------|-----------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | F. Hoffmann-La Roche AG                                                                             |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070                                                  |
| Public contact               | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact           | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.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                       | 08 February 2017 |
| Is this the analysis of the primary completion data? | No               |

|                                  |                  |
|----------------------------------|------------------|
| Global end of trial reached?     | Yes              |
| Global end of trial date         | 08 February 2017 |
| Was the trial ended prematurely? | No               |

Notes:

## General information about the trial

Main objective of the trial:

To assess long-term safety and tolerability of crenezumab administered subcutaneously (SC) every 2 weeks (q2w) or intravenously (IV) every 4 weeks (q4w), in eligible subjects with Alzheimer's disease who participated in Study ABE4869g or ABE4955g and had completed the Week 73 study visit, including brain magnetic resonance imaging (MRI).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 07 December 2012 |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety           |
| Long term follow-up duration                              | 2 Months         |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | France: 22         |
| Country: Number of subjects enrolled | Germany: 19        |
| Country: Number of subjects enrolled | Spain: 18          |
| Country: Number of subjects enrolled | United Kingdom: 26 |
| Country: Number of subjects enrolled | Canada: 69         |
| Country: Number of subjects enrolled | United States: 206 |
| Worldwide total number of subjects   | 360                |
| EEA total number of subjects         | 85                 |

Notes:

### Subjects enrolled per age group

|                                           |   |
|-------------------------------------------|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |

|                           |     |
|---------------------------|-----|
| Children (2-11 years)     | 0   |
| Adolescents (12-17 years) | 0   |
| Adults (18-64 years)      | 53  |
| From 65 to 84 years       | 306 |
| 85 years and over         | 1   |

## Subject disposition

### Recruitment

Recruitment details:

A total of 360 subjects were enrolled at 83 sites across 6 countries.

### Pre-assignment

Screening details:

Subjects who completed either Phase II Study NCT01343966 or NCT01397578 and had Mini-Mental State Examination (MMSE) score of 10 or more at the time of screening were included. A total of 360/396 subjects were enrolled and included in Safety-Evaluable Population (Assigned Treatment); 47 in Group A, 67 in Group B, 101 in Group C and 145 in Group D.

### Period 1

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

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Group A |

Arm description:

Subjects who received placebo subcutaneously (SC) on their parent study followed by Crenezumab (Cren) SC, then Cren intravenously (IV), on Study NCT01723826.

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

Dosage and administration details:

Matching placebo to crenezumab 300 milligrams (mg) subcutaneously (SC) every two weeks (q2w).

|                                        |                                        |
|----------------------------------------|----------------------------------------|
| Investigational medicinal product name | Crenezumab IV                          |
| Investigational medicinal product code |                                        |
| Other name                             |                                        |
| Pharmaceutical forms                   | Concentrate for solution for injection |
| Routes of administration               | Intravenous use                        |

Dosage and administration details:

Subjects were randomized to receive crenezumab 15 milligrams per kilogram (mg/kg) intravenously (IV) every four weeks (q4w).

|                                        |                                        |
|----------------------------------------|----------------------------------------|
| Investigational medicinal product name | Crenezumab SC                          |
| Investigational medicinal product code |                                        |
| Other name                             |                                        |
| Pharmaceutical forms                   | Concentrate for solution for injection |
| Routes of administration               | Subcutaneous use                       |

Dosage and administration details:

Subjects were randomized to receive crenezumab 300 milligrams (mg) subcutaneously (SC) every two weeks (q2w). Following the implementation of Protocol amendment, all subjects were transferred into the intravenously (IV) dosing arm and received crenezumab 15 milligrams per kilogram (mg/kg) every four weeks (q4w), starting 2-4 weeks after the last SC dose.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Group B |
|------------------|---------|

Arm description:

Subjects who received placebo intravenously (IV) on their parent study followed by Crenezumab (Cren)

IV on Study NCT01723826.

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

Dosage and administration details:

Matching placebo to crenezumab 15 milligrams per kilogram (mg/kg) intravenously (IV) every four weeks (q4w).

|                                        |                                        |
|----------------------------------------|----------------------------------------|
| Investigational medicinal product name | Crenezumab IV                          |
| Investigational medicinal product code |                                        |
| Other name                             |                                        |
| Pharmaceutical forms                   | Concentrate for solution for injection |
| Routes of administration               | Intravenous use                        |

Dosage and administration details:

Subjects were randomized to receive crenezumab 15 milligrams per kilogram (mg/kg) intravenously (IV) every four weeks (q4w).

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Group C |
|------------------|---------|

Arm description:

Subjects who received Crenezumab (Cren) subcutaneously (SC) on their parent study followed by Cren SC, then Cren intravenously (IV), on Study NCT01723826.

|                                        |                                        |
|----------------------------------------|----------------------------------------|
| Arm type                               | Experimental                           |
| Investigational medicinal product name | Crenezumab SC                          |
| Investigational medicinal product code |                                        |
| Other name                             |                                        |
| Pharmaceutical forms                   | Concentrate for solution for injection |
| Routes of administration               | Subcutaneous use                       |

Dosage and administration details:

Subjects were randomized to receive crenezumab 300 milligrams (mg) subcutaneously (SC) every two weeks (q2w). Following the implementation of Protocol amendment, all subjects were transferred into the intravenously (IV) dosing arm and received crenezumab 15 milligrams per kilogram (mg/kg) every four weeks (q4w), starting 2-4 weeks after the last SC dose.

|                                        |                                        |
|----------------------------------------|----------------------------------------|
| Investigational medicinal product name | Crenezumab IV                          |
| Investigational medicinal product code |                                        |
| Other name                             |                                        |
| Pharmaceutical forms                   | Concentrate for solution for injection |
| Routes of administration               | Intravenous use                        |

Dosage and administration details:

Subjects were randomized to receive crenezumab 15 milligrams per kilogram (mg/kg) intravenously (IV) every four weeks (q4w).

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Group D |
|------------------|---------|

Arm description:

Subjects who received Crenezumab (Cren) intravenously (IV) on their parent study followed by Cren IV on Study NCT01723826.

|                                        |                                        |
|----------------------------------------|----------------------------------------|
| Arm type                               | Experimental                           |
| Investigational medicinal product name | Crenezumab IV                          |
| Investigational medicinal product code |                                        |
| Other name                             |                                        |
| Pharmaceutical forms                   | Concentrate for solution for injection |
| Routes of administration               | Intravenous use                        |

Dosage and administration details:

Subjects were randomized to receive crenezumab 15 milligrams per kilogram (mg/kg) intravenously (IV) every four weeks (q4w).

| <b>Number of subjects in period 1</b> | Group A | Group B | Group C |
|---------------------------------------|---------|---------|---------|
| Started                               | 47      | 67      | 101     |
| Completed                             | 20      | 28      | 44      |
| Not completed                         | 27      | 39      | 57      |
| Physician decision                    | 1       | 3       | 4       |
| Death                                 | -       | 3       | 2       |
| Adverse event                         | 5       | 1       | 5       |
| Non-compliance with study drug        | -       | 1       | -       |
| Non-compliance                        | -       | 1       | 3       |
| Lost to follow-up                     | 1       | 3       | 1       |
| Reason not specified                  | 8       | 8       | 12      |
| Protocol deviation                    | 1       | 1       | 3       |
| Withdrawal by subject                 | 11      | 18      | 27      |

| <b>Number of subjects in period 1</b> | Group D |
|---------------------------------------|---------|
| Started                               | 145     |
| Completed                             | 58      |
| Not completed                         | 87      |
| Physician decision                    | 11      |
| Death                                 | 2       |
| Adverse event                         | 6       |
| Non-compliance with study drug        | -       |
| Non-compliance                        | 3       |
| Lost to follow-up                     | 1       |
| Reason not specified                  | 14      |
| Protocol deviation                    | 2       |
| Withdrawal by subject                 | 48      |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                               |         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| Reporting group title                                                                                                                                                                         | Group A |
| Reporting group description:<br>Subjects who received placebo subcutaneously (SC) on their parent study followed by Crenezumab (Cren) SC, then Cren intravenously (IV), on Study NCT01723826. |         |
| Reporting group title                                                                                                                                                                         | Group B |
| Reporting group description:<br>Subjects who received placebo intravenously (IV) on their parent study followed by Crenezumab (Cren) IV on Study NCT01723826.                                 |         |
| Reporting group title                                                                                                                                                                         | Group C |
| Reporting group description:<br>Subjects who received Crenezumab (Cren) subcutaneously (SC) on their parent study followed by Cren SC, then Cren intravenously (IV), on Study NCT01723826.    |         |
| Reporting group title                                                                                                                                                                         | Group D |
| Reporting group description:<br>Subjects who received Crenezumab (Cren) intravenously (IV) on their parent study followed by Cren IV on Study NCT01723826.                                    |         |

| Reporting group values             | Group A | Group B | Group C |
|------------------------------------|---------|---------|---------|
| Number of subjects                 | 47      | 67      | 101     |
| Age Categorical<br>Units: Subjects |         |         |         |

|                                       |       |       |       |
|---------------------------------------|-------|-------|-------|
| Age Continuous<br>Units: years        |       |       |       |
| arithmetic mean                       | 70.9  | 71.9  | 72.3  |
| standard deviation                    | ± 7.4 | ± 7.5 | ± 7.2 |
| Gender Categorical<br>Units: Subjects |       |       |       |
| Female                                | 26    | 38    | 58    |
| Male                                  | 21    | 29    | 43    |

| Reporting group values             | Group D | Total |  |
|------------------------------------|---------|-------|--|
| Number of subjects                 | 145     | 360   |  |
| Age Categorical<br>Units: Subjects |         |       |  |

|                                       |       |     |  |
|---------------------------------------|-------|-----|--|
| Age Continuous<br>Units: years        |       |     |  |
| arithmetic mean                       | 72.2  |     |  |
| standard deviation                    | ± 6.6 | -   |  |
| Gender Categorical<br>Units: Subjects |       |     |  |
| Female                                | 77    | 199 |  |
| Male                                  | 68    | 161 |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                       |                               |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                 | Group A                       |
| Reporting group description:<br>Subjects who received placebo subcutaneously (SC) on their parent study followed by Crenezumab (Cren) SC, then Cren intravenously (IV), on Study NCT01723826.                                                                                         |                               |
| Reporting group title                                                                                                                                                                                                                                                                 | Group B                       |
| Reporting group description:<br>Subjects who received placebo intravenously (IV) on their parent study followed by Crenezumab (Cren) IV on Study NCT01723826.                                                                                                                         |                               |
| Reporting group title                                                                                                                                                                                                                                                                 | Group C                       |
| Reporting group description:<br>Subjects who received Crenezumab (Cren) subcutaneously (SC) on their parent study followed by Cren SC, then Cren intravenously (IV), on Study NCT01723826.                                                                                            |                               |
| Reporting group title                                                                                                                                                                                                                                                                 | Group D                       |
| Reporting group description:<br>Subjects who received Crenezumab (Cren) intravenously (IV) on their parent study followed by Cren IV on Study NCT01723826.                                                                                                                            |                               |
| Subject analysis set title                                                                                                                                                                                                                                                            | PCP PL SC OLE CREN SC to IV   |
| Subject analysis set type                                                                                                                                                                                                                                                             | Safety analysis               |
| Subject analysis set description:<br>Subject Analysis Set represents the population who received the treatment and were used for safety analysis. Here, PCP= Placebo-controlled portion; PL= Placebo; SC= Subcutaneous; OLE= Open-label extension; CREN= Crenezumab; IV= Intravenous. |                               |
| Subject analysis set title                                                                                                                                                                                                                                                            | PCP PL IV OLE CREN IV         |
| Subject analysis set type                                                                                                                                                                                                                                                             | Safety analysis               |
| Subject analysis set description:<br>Subject Analysis Set represents the population who received the treatment and were used for safety analysis. Here, PCP= Placebo-controlled portion; PL= Placebo; OLE= Open-label extension; CREN= Crenezumab; IV= Intravenous.                   |                               |
| Subject analysis set title                                                                                                                                                                                                                                                            | PCP CREN SC OLE CREN SC to IV |
| Subject analysis set type                                                                                                                                                                                                                                                             | Safety analysis               |
| Subject analysis set description:<br>Subject Analysis Set represents the population who received the treatment and were used for safety analysis. Here, PCP= Placebo-controlled portion; PL= Placebo; SC= Subcutaneous; OLE= Open-label extension; CREN= Crenezumab; IV= Intravenous. |                               |
| Subject analysis set title                                                                                                                                                                                                                                                            | PCP CREN IV OLE CREN IV       |
| Subject analysis set type                                                                                                                                                                                                                                                             | Safety analysis               |
| Subject analysis set description:<br>Subject Analysis Set represents the population who received the treatment and were used for safety analysis. Here, PCP= Placebo-controlled portion; PL= Placebo; OLE= Open-label extension; CREN= Crenezumab; IV= Intravenous.                   |                               |

### Primary: Percentage of Subjects with Adverse Events (AE)

|                                                                                                                                                                                                                                                                                                            |                                                                |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                            | Percentage of Subjects with Adverse Events (AE) <sup>[1]</sup> |
| End point description:<br>An AE was defined as any untoward medical occurrence in a subject administered a pharmaceutical product which does not necessarily have a causal relationship with the treatment. Safety Analysis population included all subjects who received at least one dose of study drug. |                                                                |
| End point type                                                                                                                                                                                                                                                                                             | Primary                                                        |
| End point timeframe:<br>Up to 50 months                                                                                                                                                                                                                                                                    |                                                                |

Notes:

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

Justification: Only descriptive analysis was planned to be reported.

| End point values              | PCP PL SC OLE<br>CREN SC to IV | PCP PL IV OLE<br>CREN IV | PCP CREN SC<br>OLE CREN SC<br>to IV | PCP CREN IV<br>OLE CREN IV |
|-------------------------------|--------------------------------|--------------------------|-------------------------------------|----------------------------|
| Subject group type            | Subject analysis set           | Subject analysis set     | Subject analysis set                | Subject analysis set       |
| Number of subjects analysed   | 47                             | 63                       | 101                                 | 149                        |
| Units: percentage of subjects |                                |                          |                                     |                            |
| number (not applicable)       | 89.4                           | 90.5                     | 96.0                                | 87.9                       |

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects by Nature of Adverse Events

|                 |                                                                   |
|-----------------|-------------------------------------------------------------------|
| End point title | Percentage of Subjects by Nature of Adverse Events <sup>[2]</sup> |
|-----------------|-------------------------------------------------------------------|

End point description:

A serious adverse event is any AE that meets any of the following criteria: fatal, life threatening, requires or prolongs inpatient hospitalization, results in persistent or significant disability/incapacity, congenital anomaly/birth defect in a neonate/infant. Non-Serious Adverse events of special interest for this study include the following: cerebral vascular edema, Superficial siderosis of central nervous system, cerebral micro-hemorrhages or macro-hemorrhages, pneumonia, liver injury. Safety Analysis population included all subjects who received at least one dose of study drug.

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

End point timeframe:

Up to 50 months

Notes:

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

Justification: Only descriptive analysis was planned to be reported.

| End point values                     | PCP PL SC OLE<br>CREN SC to IV | PCP PL IV OLE<br>CREN IV | PCP CREN SC<br>OLE CREN SC<br>to IV | PCP CREN IV<br>OLE CREN IV |
|--------------------------------------|--------------------------------|--------------------------|-------------------------------------|----------------------------|
| Subject group type                   | Subject analysis set           | Subject analysis set     | Subject analysis set                | Subject analysis set       |
| Number of subjects analysed          | 47                             | 63                       | 101                                 | 149                        |
| Units: percentage of subjects        |                                |                          |                                     |                            |
| number (not applicable)              |                                |                          |                                     |                            |
| Serious Adverse Events (SAE)         | 19.1                           | 22.2                     | 21.8                                | 23.5                       |
| Non-Serious Adverse Events (Non-SAE) | 87.2                           | 88.9                     | 94.1                                | 87.2                       |

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects by Severity of Adverse Events

|                 |                                                                     |
|-----------------|---------------------------------------------------------------------|
| End point title | Percentage of Subjects by Severity of Adverse Events <sup>[3]</sup> |
|-----------------|---------------------------------------------------------------------|

End point description:

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

End point timeframe:

Up to 50 months

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 analysis was planned to be reported.

| End point values              | PCP PL SC OLE<br>CREN SC to IV | PCP PL IV OLE<br>CREN IV | PCP CREN SC<br>OLE CREN SC<br>to IV | PCP CREN IV<br>OLE CREN IV |
|-------------------------------|--------------------------------|--------------------------|-------------------------------------|----------------------------|
| Subject group type            | Subject analysis set           | Subject analysis set     | Subject analysis set                | Subject analysis set       |
| Number of subjects analysed   | 47                             | 63                       | 101                                 | 149                        |
| Units: percentage of subjects |                                |                          |                                     |                            |
| number (not applicable)       |                                |                          |                                     |                            |
| Grade 1                       | 19.1                           | 34.9                     | 29.7                                | 22.1                       |
| Grade 2                       | 44.7                           | 31.7                     | 43.6                                | 40.3                       |
| Grade 3                       | 12.8                           | 17.5                     | 16.8                                | 19.5                       |
| Grade 4                       | 8.5                            | 1.6                      | 3.0                                 | 1.3                        |
| Grade 5                       | 4.3                            | 4.8                      | 3.0                                 | 4.7                        |

## Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Subjects with Human Anti-Therapeutic Antibody (ATA) Formation

|                 |                                                                                            |
|-----------------|--------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects with Human Anti-Therapeutic Antibody (ATA) Formation <sup>[4]</sup> |
|-----------------|--------------------------------------------------------------------------------------------|

End point description:

Anti-therapeutic antibodies (ATA), a measurement to explore the potential relationship of immunogenicity response with pharmacokinetics, safety and efficacy. Percentage of participants at post-baseline with positive results for ATA against crenezumab are reported. Safety Analysis population included all subjects who received at least one dose of study drug.

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

End point timeframe:

Pre-dose (Day-14), predose at Week 25, 49, 97, Follow-up Week 8 (Week 153) and 12 (Week 157)

Notes:

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

Justification: Only descriptive analysis was planned to be reported.

| End point values              | PCP PL SC OLE<br>CREN SC to IV | PCP PL IV OLE<br>CREN IV | PCP CREN SC<br>OLE CREN SC<br>to IV | PCP CREN IV<br>OLE CREN IV |
|-------------------------------|--------------------------------|--------------------------|-------------------------------------|----------------------------|
| Subject group type            | Subject analysis set           | Subject analysis set     | Subject analysis set                | Subject analysis set       |
| Number of subjects analysed   | 47                             | 63                       | 101                                 | 149                        |
| Units: percentage of subjects |                                |                          |                                     |                            |
| number (not applicable)       | 9.1                            | 3.4                      | 9.1                                 | 0.7                        |

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects with Amyloid-Related Imaging Abnormalities-Edema/Effusions (ARIA-E)

|                 |                                                                                                           |
|-----------------|-----------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects with Amyloid-Related Imaging Abnormalities-Edema/Effusions (ARIA-E) <sup>[5]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------|

End point description:

Alzheimer's disease (AD) is associated with amyloid-related imaging abnormalities (ARIA). The occurrence of imaging abnormalities believed to represent cerebral vasogenic edema, has been reported in association with the investigational use of compounds that are intended to treat Alzheimer's disease by reducing Aβ in the brain. Here, the percentage of subjects with symptomatic and asymptomatic ARIA-E were reported. Safety Analysis population included all subjects who received at least one dose of study drug.

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

End point timeframe:

Baseline, Weeks 23, 47, 71, 97, 121 and 153

Notes:

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

Justification: Only descriptive analysis was planned to be reported.

| End point values              | PCP PL SC OLE<br>CREN SC to IV | PCP PL IV OLE<br>CREN IV | PCP CREN SC<br>OLE CREN SC<br>to IV | PCP CREN IV<br>OLE CREN IV |
|-------------------------------|--------------------------------|--------------------------|-------------------------------------|----------------------------|
| Subject group type            | Subject analysis set           | Subject analysis set     | Subject analysis set                | Subject analysis set       |
| Number of subjects analysed   | 47                             | 63                       | 101                                 | 149                        |
| Units: percentage of subjects |                                |                          |                                     |                            |
| number (not applicable)       |                                |                          |                                     |                            |
| Symptomatic                   | 0                              | 0                        | 0                                   | 0                          |
| Asymptomatic                  | 0                              | 0                        | 0                                   | 0.7                        |

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects with Amyloid-Related Imaging Abnormalities-Hemorrhage (ARIA-H)

|                 |                                                                                                      |
|-----------------|------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects with Amyloid-Related Imaging Abnormalities-Hemorrhage (ARIA-H) <sup>[6]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------|

End point description:

Alzheimer's disease (AD) is associated with amyloid-related imaging abnormalities (ARIA). Cerebral micro-hemorrhages (microbleeds [MBs]) are radiologically defined as small dot-like foci of signal loss observed on MRI sequences sensitive for paramagnetic tissue properties. The occurrence of MBs has also been identified as an adverse event in anti-amyloid vaccination trials, and together with superficial siderosis, they have been termed "amyloid-related imaging abnormalities-hemorrhage (ARIA-H). Safety

Analysis population included all subjects who received at least one dose of study drug.

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

End point timeframe:

Baseline, Weeks 23, 47, 71, 97, 121 and 153

Notes:

[6] - 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 analysis was planned to be reported.

| End point values              | PCP PL SC OLE<br>CREN SC to IV | PCP PL IV OLE<br>CREN IV | PCP CREN SC<br>OLE CREN SC<br>to IV | PCP CREN IV<br>OLE CREN IV |
|-------------------------------|--------------------------------|--------------------------|-------------------------------------|----------------------------|
| Subject group type            | Subject analysis set           | Subject analysis set     | Subject analysis set                | Subject analysis set       |
| Number of subjects analysed   | 47                             | 63                       | 101                                 | 149                        |
| Units: percentage of subjects |                                |                          |                                     |                            |
| number (not applicable)       |                                |                          |                                     |                            |
| Superficial Siderosis         | 2.1                            | 0                        | 3.0                                 | 0.7                        |
| New Micro-hemorrhage          | 6.4                            | 9.5                      | 4.0                                 | 6.0                        |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 50 months

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

### Reporting groups

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | PCP PL SC OLE CREN SC to IV |
|-----------------------|-----------------------------|

Reporting group description:

Subject Analysis Set represents the population who received the treatment and were used for all safety analyses. Here, PCP= Placebo-controlled portion; PL= Placebo; SC= Subcutaneous; OLE= Open-label extension; CREN= Crenezumab; IV= Intravenous.

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | PCP PL IV OLE CREN IV |
|-----------------------|-----------------------|

Reporting group description:

Subject Analysis Set represents the population who received the treatment and were used for all safety analyses. Here, PCP= Placebo-controlled portion; PL= Placebo; OLE= Open-label extension; CREN= Crenezumab; IV= Intravenous.

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | PCP CREN SC OLE CREN SC to IV |
|-----------------------|-------------------------------|

Reporting group description:

Subject Analysis Set represents the population who received the treatment and were used for all safety analyses. Here, PCP= Placebo-controlled portion; PL= Placebo; SC= Subcutaneous; OLE= Open-label extension; CREN= Crenezumab; IV= Intravenous.

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | PCP CREN IV OLE CREN IV |
|-----------------------|-------------------------|

Reporting group description:

Subject Analysis Set represents the population who received the treatment and were used for all safety analyses. Here, PCP= Placebo-controlled portion; PL= Placebo; OLE= Open-label extension; CREN= Crenezumab; IV= Intravenous.

| Serious adverse events                                              | PCP PL SC OLE<br>CREN SC to IV | PCP PL IV OLE CREN<br>IV | PCP CREN SC OLE<br>CREN SC to IV |
|---------------------------------------------------------------------|--------------------------------|--------------------------|----------------------------------|
| Total subjects affected by serious adverse events                   |                                |                          |                                  |
| subjects affected / exposed                                         | 9 / 47 (19.15%)                | 14 / 63 (22.22%)         | 22 / 101 (21.78%)                |
| number of deaths (all causes)                                       | 2                              | 3                        | 3                                |
| number of deaths resulting from adverse events                      |                                |                          |                                  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                |                          |                                  |
| Basal cell carcinoma                                                |                                |                          |                                  |
| subjects affected / exposed                                         | 0 / 47 (0.00%)                 | 1 / 63 (1.59%)           | 0 / 101 (0.00%)                  |
| occurrences causally related to treatment / all                     | 0 / 0                          | 0 / 1                    | 0 / 0                            |
| deaths causally related to treatment / all                          | 0 / 0                          | 0 / 0                    | 0 / 0                            |
| Colon cancer                                                        |                                |                          |                                  |

|                                                 |                |                |                 |
|-------------------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Intestinal adenocarcinoma                       |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| Metastatic neoplasm                             |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 1 / 63 (1.59%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Prostate cancer                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 1 / 63 (1.59%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Vascular disorders                              |                |                |                 |
| Aortic aneurysm                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Deep vein thrombosis                            |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Exsanguination                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Hypertension                                    |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 1 / 63 (1.59%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Hypotension                                     |                |                |                 |

|                                                      |                |                |                 |
|------------------------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed                          | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 2 / 101 (1.98%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Phlebitis                                            |                |                |                 |
| subjects affected / exposed                          | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| General disorders and administration site conditions |                |                |                 |
| Asthenia                                             |                |                |                 |
| subjects affected / exposed                          | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Chest pain                                           |                |                |                 |
| subjects affected / exposed                          | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Death                                                |                |                |                 |
| subjects affected / exposed                          | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Gait disturbance                                     |                |                |                 |
| subjects affected / exposed                          | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Incarcerated hernia                                  |                |                |                 |
| subjects affected / exposed                          | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders      |                |                |                 |
| Acute respiratory failure                            |                |                |                 |
| subjects affected / exposed                          | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |

|                                                 |                |                |                 |
|-------------------------------------------------|----------------|----------------|-----------------|
| Pulmonary granuloma                             |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Tachypnoea                                      |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Psychiatric disorders                           |                |                |                 |
| Abnormal behaviour                              |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 1 / 63 (1.59%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Aggression                                      |                |                |                 |
| subjects affected / exposed                     | 1 / 47 (2.13%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Agitation                                       |                |                |                 |
| subjects affected / exposed                     | 1 / 47 (2.13%) | 1 / 63 (1.59%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Delirium                                        |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 1 / 63 (1.59%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| Disorientation                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Mental status changes                           |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 2 / 101 (1.98%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Psychotic disorder                              |                |                |                 |

|                                                 |                |                |                 |
|-------------------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Product issues                                  |                |                |                 |
| Device dislocation                              |                |                |                 |
| subjects affected / exposed                     | 1 / 47 (2.13%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Device failure                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 1 / 63 (1.59%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Injury, poisoning and procedural complications  |                |                |                 |
| Ankle fracture                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Cervical vertebral fracture                     |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Facial bones fracture                           |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Fall                                            |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 1 / 63 (1.59%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Femoral neck fracture                           |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 1 / 63 (1.59%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |

|                                                 |                |                |                 |
|-------------------------------------------------|----------------|----------------|-----------------|
| Femur fracture                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 1 / 63 (1.59%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Fracture displacement                           |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Fractured sacrum                                |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Hip fracture                                    |                |                |                 |
| subjects affected / exposed                     | 1 / 47 (2.13%) | 1 / 63 (1.59%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Humerus fracture                                |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Laceration                                      |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Limb injury                                     |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pelvic fracture                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Subarachnoid haemorrhage                        |                |                |                 |

|                                                 |                |                |                 |
|-------------------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 47 (0.00%) | 1 / 63 (1.59%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Subdural haematoma                              |                |                |                 |
| subjects affected / exposed                     | 2 / 47 (4.26%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Thoracic vertebral fracture                     |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 1 / 63 (1.59%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Wrist fracture                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Cardiac disorders                               |                |                |                 |
| Acute myocardial infarction                     |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Atrial fibrillation                             |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Atrial flutter                                  |                |                |                 |
| subjects affected / exposed                     | 1 / 47 (2.13%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Cardio-respiratory arrest                       |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Myocardial infarction                           |                |                |                 |

|                                                 |                |                |                 |
|-------------------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| Sinus tachycardia                               |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Nervous system disorders                        |                |                |                 |
| Basilar artery stenosis                         |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Cerebrovascular accident                        |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Dementia                                        |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 2 / 63 (3.17%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0           |
| Dementia alzheimer's type                       |                |                |                 |
| subjects affected / exposed                     | 2 / 47 (4.26%) | 2 / 63 (3.17%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 2          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 2          | 0 / 2          | 0 / 0           |
| Dementia with lewy bodies                       |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Depressed level of consciousness                |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Dizziness                                       |                |                |                 |

|                                                 |                |                |                 |
|-------------------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Encephalopathy                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Epilepsy                                        |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Generalised tonic-clonic seizure                |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Hydrocephalus                                   |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 1 / 63 (1.59%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Ischaemic stroke                                |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Metabolic encephalopathy                        |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Paraesthesia                                    |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Presyncope                                      |                |                |                 |

|                                                 |                |                |                 |
|-------------------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 2 / 101 (1.98%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Seizure                                         |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 1 / 63 (1.59%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Syncope                                         |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 2 / 63 (3.17%) | 3 / 101 (2.97%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Transient ischaemic attack                      |                |                |                 |
| subjects affected / exposed                     | 1 / 47 (2.13%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Blood and lymphatic system disorders            |                |                |                 |
| Anaemia                                         |                |                |                 |
| alternative dictionary used: MedDRA 20.0        |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Neutropenia                                     |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Ear and labyrinth disorders                     |                |                |                 |
| Vertigo                                         |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 1 / 63 (1.59%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Gastrointestinal disorders                      |                |                |                 |
| Abdominal pain                                  |                |                |                 |

|                                                 |                |                |                 |
|-------------------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Inguinal hernia                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Intestinal obstruction                          |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Nausea                                          |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Small intestinal obstruction                    |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Vomiting                                        |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Hepatobiliary disorders                         |                |                |                 |
| Biliary colic                                   |                |                |                 |
| subjects affected / exposed                     | 1 / 47 (2.13%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Cholelithiasis                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Renal and urinary disorders                     |                |                |                 |

|                                                 |                |                |                 |
|-------------------------------------------------|----------------|----------------|-----------------|
| Acute prerenal failure                          |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Urinary retention                               |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                |                |                 |
| Back pain                                       |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 1 / 63 (1.59%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Osteoarthritis                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Infections and infestations                     |                |                |                 |
| Bacteraemia                                     |                |                |                 |
| subjects affected / exposed                     | 1 / 47 (2.13%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Diverticulitis                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Escherichia urinary tract infection             |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 2 / 101 (1.98%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Gastroenteritis                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |

|                                                 |                |                |                 |
|-------------------------------------------------|----------------|----------------|-----------------|
| Influenza                                       |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Osteomyelitis                                   |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pneumonia                                       |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 1 / 63 (1.59%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pneumonia bacterial                             |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pneumonia escherichia                           |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pneumonia viral                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Post procedural infection                       |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Sepsis                                          |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Septic shock                                    |                |                |                 |

|                                                 |                |                |                 |
|-------------------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Upper respiratory tract infection               |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Urinary tract infection                         |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 2 / 101 (1.98%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Urosepsis                                       |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 1 / 63 (1.59%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Metabolism and nutrition disorders              |                |                |                 |
| Adult failure to thrive                         |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Dehydration                                     |                |                |                 |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 63 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |

|                                                                     |                            |  |  |
|---------------------------------------------------------------------|----------------------------|--|--|
| <b>Serious adverse events</b>                                       | PCP CREN IV OLE<br>CREN IV |  |  |
| Total subjects affected by serious adverse events                   |                            |  |  |
| subjects affected / exposed                                         | 35 / 149 (23.49%)          |  |  |
| number of deaths (all causes)                                       | 7                          |  |  |
| number of deaths resulting from adverse events                      |                            |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                            |  |  |
| Basal cell carcinoma                                                |                            |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Colon cancer                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intestinal adenocarcinoma                       |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metastatic neoplasm                             |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Prostate cancer                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vascular disorders                              |                 |  |  |
| Aortic aneurysm                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Deep vein thrombosis                            |                 |  |  |
| subjects affected / exposed                     | 2 / 149 (1.34%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Exsanguination                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Hypertension                                    |                 |  |  |

|                                                      |                 |  |  |
|------------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                          | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Hypotension                                          |                 |  |  |
| subjects affected / exposed                          | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Phlebitis                                            |                 |  |  |
| subjects affected / exposed                          | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Asthenia                                             |                 |  |  |
| subjects affected / exposed                          | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Chest pain                                           |                 |  |  |
| subjects affected / exposed                          | 2 / 149 (1.34%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Death                                                |                 |  |  |
| subjects affected / exposed                          | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 1           |  |  |
| Gait disturbance                                     |                 |  |  |
| subjects affected / exposed                          | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Incarcerated hernia                                  |                 |  |  |
| subjects affected / exposed                          | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders      |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| Acute respiratory failure                       |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary granuloma                             |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tachypnoea                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychiatric disorders                           |                 |  |  |
| Abnormal behaviour                              |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Aggression                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Agitation                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Delirium                                        |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Disorientation                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Mental status changes                           |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychotic disorder                              |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Product issues                                  |                 |  |  |
| Device dislocation                              |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Device failure                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| Ankle fracture                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cervical vertebral fracture                     |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Facial bones fracture                           |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Fall                                            |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| Femoral neck fracture                           |                 |  |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Femur fracture                                  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Fracture displacement                           |                 |  |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Fractured sacrum                                |                 |  |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Hip fracture                                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Humerus fracture                                |                 |  |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Laceration                                      |                 |  |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Limb injury                                     |                 |  |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pelvic fracture                                 |                 |  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Subarachnoid haemorrhage                        |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Subdural haematoma                              |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Thoracic vertebral fracture                     |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Wrist fracture                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Acute myocardial infarction                     |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atrial fibrillation                             |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atrial flutter                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardio-respiratory arrest                       |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Myocardial infarction                           |                 |  |  |
| subjects affected / exposed                     | 2 / 149 (1.34%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Sinus tachycardia                               |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nervous system disorders                        |                 |  |  |
| Basilar artery stenosis                         |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cerebrovascular accident                        |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dementia                                        |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dementia alzheimer's type                       |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Dementia with lewy bodies                       |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Depressed level of consciousness                |                 |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Dizziness                                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Encephalopathy                                  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Epilepsy                                        |                 |  |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Generalised tonic-clonic seizure                |                 |  |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Hydrocephalus                                   |                 |  |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Ischaemic stroke                                |                 |  |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Metabolic encephalopathy                        |                 |  |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Paraesthesia                                    |                 |  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Presyncope                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Seizure                                         |                 |  |  |
| subjects affected / exposed                     | 2 / 149 (1.34%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Syncope                                         |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Transient ischaemic attack                      |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood and lymphatic system disorders            |                 |  |  |
| Anaemia                                         |                 |  |  |
| alternative dictionary used: MedDRA 20.0        |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Neutropenia                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ear and labyrinth disorders                     |                 |  |  |
| Vertigo                                         |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| Gastrointestinal disorders                      |                 |  |  |
| Abdominal pain                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Inguinal hernia                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intestinal obstruction                          |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nausea                                          |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Small intestinal obstruction                    |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vomiting                                        |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| Biliary colic                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cholelithiasis                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| Renal and urinary disorders                     |                 |  |  |
| Acute prerenal failure                          |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urinary retention                               |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Back pain                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Osteoarthritis                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Bacteraemia                                     |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Diverticulitis                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Escherichia urinary tract infection             |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastroenteritis                                 |                 |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Influenza                                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Osteomyelitis                                   |                 |  |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumonia                                       |                 |  |  |  |
| subjects affected / exposed                     | 3 / 149 (2.01%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 5           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Pneumonia bacterial                             |                 |  |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumonia escherichia                           |                 |  |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumonia viral                                 |                 |  |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Post procedural infection                       |                 |  |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Sepsis                                          |                 |  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Septic shock                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Upper respiratory tract infection               |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urinary tract infection                         |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urosepsis                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Adult failure to thrive                         |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Dehydration                                     |                 |  |  |
| subjects affected / exposed                     | 3 / 149 (2.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

| <b>Non-serious adverse events</b>                                   | PCP PL SC OLE<br>CREN SC to IV | PCP PL IV OLE CREN<br>IV | PCP CREN SC OLE<br>CREN SC to IV |
|---------------------------------------------------------------------|--------------------------------|--------------------------|----------------------------------|
| Total subjects affected by non-serious adverse events               |                                |                          |                                  |
| subjects affected / exposed                                         | 37 / 47 (78.72%)               | 51 / 63 (80.95%)         | 80 / 101 (79.21%)                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                |                          |                                  |
| Squamous cell carcinoma                                             |                                |                          |                                  |
| subjects affected / exposed                                         | 3 / 47 (6.38%)                 | 1 / 63 (1.59%)           | 2 / 101 (1.98%)                  |
| occurrences (all)                                                   | 8                              | 1                        | 2                                |
| Vascular disorders                                                  |                                |                          |                                  |
| Haematoma                                                           |                                |                          |                                  |
| subjects affected / exposed                                         | 3 / 47 (6.38%)                 | 2 / 63 (3.17%)           | 2 / 101 (1.98%)                  |
| occurrences (all)                                                   | 3                              | 2                        | 2                                |
| General disorders and administration site conditions                |                                |                          |                                  |
| Fatigue                                                             |                                |                          |                                  |
| subjects affected / exposed                                         | 2 / 47 (4.26%)                 | 0 / 63 (0.00%)           | 8 / 101 (7.92%)                  |
| occurrences (all)                                                   | 2                              | 0                        | 8                                |
| Injection site erythema                                             |                                |                          |                                  |
| subjects affected / exposed                                         | 2 / 47 (4.26%)                 | 1 / 63 (1.59%)           | 8 / 101 (7.92%)                  |
| occurrences (all)                                                   | 13                             | 1                        | 10                               |
| Injection site extravasation                                        |                                |                          |                                  |
| subjects affected / exposed                                         | 3 / 47 (6.38%)                 | 1 / 63 (1.59%)           | 3 / 101 (2.97%)                  |
| occurrences (all)                                                   | 5                              | 1                        | 7                                |
| Respiratory, thoracic and mediastinal disorders                     |                                |                          |                                  |
| Cough                                                               |                                |                          |                                  |
| subjects affected / exposed                                         | 5 / 47 (10.64%)                | 3 / 63 (4.76%)           | 8 / 101 (7.92%)                  |
| occurrences (all)                                                   | 11                             | 3                        | 9                                |
| Psychiatric disorders                                               |                                |                          |                                  |
| Agitation                                                           |                                |                          |                                  |
| subjects affected / exposed                                         | 9 / 47 (19.15%)                | 4 / 63 (6.35%)           | 13 / 101 (12.87%)                |
| occurrences (all)                                                   | 9                              | 4                        | 20                               |
| Anxiety                                                             |                                |                          |                                  |
| subjects affected / exposed                                         | 1 / 47 (2.13%)                 | 4 / 63 (6.35%)           | 8 / 101 (7.92%)                  |
| occurrences (all)                                                   | 1                              | 4                        | 9                                |
| Depression                                                          |                                |                          |                                  |
| subjects affected / exposed                                         | 3 / 47 (6.38%)                 | 8 / 63 (12.70%)          | 5 / 101 (4.95%)                  |
| occurrences (all)                                                   | 3                              | 9                        | 5                                |
| Insomnia                                                            |                                |                          |                                  |

|                                                                                                            |                       |                       |                         |
|------------------------------------------------------------------------------------------------------------|-----------------------|-----------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)                                                           | 3 / 47 (6.38%)<br>6   | 1 / 63 (1.59%)<br>1   | 8 / 101 (7.92%)<br>10   |
| Delusion<br>subjects affected / exposed<br>occurrences (all)                                               | 3 / 47 (6.38%)<br>3   | 1 / 63 (1.59%)<br>1   | 7 / 101 (6.93%)<br>7    |
| Confusional state<br>subjects affected / exposed<br>occurrences (all)                                      | 3 / 47 (6.38%)<br>3   | 1 / 63 (1.59%)<br>1   | 3 / 101 (2.97%)<br>4    |
| Investigations<br>Weight decreased<br>subjects affected / exposed<br>occurrences (all)                     | 4 / 47 (8.51%)<br>4   | 2 / 63 (3.17%)<br>2   | 8 / 101 (7.92%)<br>11   |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all) | 7 / 47 (14.89%)<br>10 | 8 / 63 (12.70%)<br>11 | 26 / 101 (25.74%)<br>42 |
| Laceration<br>subjects affected / exposed<br>occurrences (all)                                             | 3 / 47 (6.38%)<br>3   | 2 / 63 (3.17%)<br>3   | 10 / 101 (9.90%)<br>11  |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                                              | 2 / 47 (4.26%)<br>6   | 2 / 63 (3.17%)<br>2   | 6 / 101 (5.94%)<br>8    |
| Skin abrasion<br>subjects affected / exposed<br>occurrences (all)                                          | 0 / 47 (0.00%)<br>0   | 4 / 63 (6.35%)<br>4   | 5 / 101 (4.95%)<br>5    |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)                  | 2 / 47 (4.26%)<br>2   | 5 / 63 (7.94%)<br>5   | 11 / 101 (10.89%)<br>14 |
| Cerebral microhaemorrhage<br>subjects affected / exposed<br>occurrences (all)                              | 3 / 47 (6.38%)<br>3   | 4 / 63 (6.35%)<br>5   | 3 / 101 (2.97%)<br>3    |
| Headache<br>subjects affected / exposed<br>occurrences (all)                                               | 1 / 47 (2.13%)<br>1   | 2 / 63 (3.17%)<br>2   | 8 / 101 (7.92%)<br>10   |
| Gastrointestinal disorders                                                                                 |                       |                       |                         |

|                                                                                                                   |                      |                       |                         |
|-------------------------------------------------------------------------------------------------------------------|----------------------|-----------------------|-------------------------|
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                                     | 6 / 47 (12.77%)<br>7 | 3 / 63 (4.76%)<br>3   | 11 / 101 (10.89%)<br>12 |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                                      | 0 / 47 (0.00%)<br>0  | 3 / 63 (4.76%)<br>5   | 5 / 101 (4.95%)<br>6    |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                                  | 0 / 47 (0.00%)<br>0  | 4 / 63 (6.35%)<br>4   | 3 / 101 (2.97%)<br>3    |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all)                | 2 / 47 (4.26%)<br>7  | 5 / 63 (7.94%)<br>5   | 2 / 101 (1.98%)<br>2    |
| Renal and urinary disorders<br>Urinary incontinence<br>subjects affected / exposed<br>occurrences (all)           | 4 / 47 (8.51%)<br>4  | 0 / 63 (0.00%)<br>0   | 5 / 101 (4.95%)<br>6    |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 2 / 47 (4.26%)<br>4  | 5 / 63 (7.94%)<br>6   | 8 / 101 (7.92%)<br>10   |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                                                     | 3 / 47 (6.38%)<br>3  | 4 / 63 (6.35%)<br>5   | 7 / 101 (6.93%)<br>7    |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)                                                 | 3 / 47 (6.38%)<br>3  | 0 / 63 (0.00%)<br>0   | 4 / 101 (3.96%)<br>6    |
| Tendonitis<br>subjects affected / exposed<br>occurrences (all)                                                    | 3 / 47 (6.38%)<br>3  | 2 / 63 (3.17%)<br>2   | 1 / 101 (0.99%)<br>1    |
| Infections and infestations<br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)        | 7 / 47 (14.89%)<br>8 | 9 / 63 (14.29%)<br>13 | 16 / 101 (15.84%)<br>23 |
| Viral upper respiratory tract infection                                                                           |                      |                       |                         |

|                                   |                 |                  |                   |
|-----------------------------------|-----------------|------------------|-------------------|
| subjects affected / exposed       | 5 / 47 (10.64%) | 11 / 63 (17.46%) | 10 / 101 (9.90%)  |
| occurrences (all)                 | 7               | 14               | 11                |
| Upper respiratory tract infection |                 |                  |                   |
| subjects affected / exposed       | 6 / 47 (12.77%) | 5 / 63 (7.94%)   | 15 / 101 (14.85%) |
| occurrences (all)                 | 7               | 5                | 20                |
| Bronchitis                        |                 |                  |                   |
| subjects affected / exposed       | 2 / 47 (4.26%)  | 2 / 63 (3.17%)   | 4 / 101 (3.96%)   |
| occurrences (all)                 | 2               | 2                | 5                 |

|                                                                     |                            |  |  |
|---------------------------------------------------------------------|----------------------------|--|--|
| <b>Non-serious adverse events</b>                                   | PCP CREN IV OLE<br>CREN IV |  |  |
| Total subjects affected by non-serious adverse events               |                            |  |  |
| subjects affected / exposed                                         | 97 / 149 (65.10%)          |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                            |  |  |
| Squamous cell carcinoma                                             |                            |  |  |
| subjects affected / exposed                                         | 0 / 149 (0.00%)            |  |  |
| occurrences (all)                                                   | 0                          |  |  |
| Vascular disorders                                                  |                            |  |  |
| Haematoma                                                           |                            |  |  |
| subjects affected / exposed                                         | 3 / 149 (2.01%)            |  |  |
| occurrences (all)                                                   | 3                          |  |  |
| General disorders and administration site conditions                |                            |  |  |
| Fatigue                                                             |                            |  |  |
| subjects affected / exposed                                         | 4 / 149 (2.68%)            |  |  |
| occurrences (all)                                                   | 4                          |  |  |
| Injection site erythema                                             |                            |  |  |
| subjects affected / exposed                                         | 2 / 149 (1.34%)            |  |  |
| occurrences (all)                                                   | 2                          |  |  |
| Injection site extravasation                                        |                            |  |  |
| subjects affected / exposed                                         | 4 / 149 (2.68%)            |  |  |
| occurrences (all)                                                   | 16                         |  |  |
| Respiratory, thoracic and mediastinal disorders                     |                            |  |  |
| Cough                                                               |                            |  |  |
| subjects affected / exposed                                         | 11 / 149 (7.38%)           |  |  |
| occurrences (all)                                                   | 13                         |  |  |
| Psychiatric disorders                                               |                            |  |  |

|                                                                                                            |                         |  |  |
|------------------------------------------------------------------------------------------------------------|-------------------------|--|--|
| Agitation<br>subjects affected / exposed<br>occurrences (all)                                              | 13 / 149 (8.72%)<br>14  |  |  |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                                                | 15 / 149 (10.07%)<br>16 |  |  |
| Depression<br>subjects affected / exposed<br>occurrences (all)                                             | 7 / 149 (4.70%)<br>7    |  |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                                               | 8 / 149 (5.37%)<br>9    |  |  |
| Delusion<br>subjects affected / exposed<br>occurrences (all)                                               | 4 / 149 (2.68%)<br>6    |  |  |
| Confusional state<br>subjects affected / exposed<br>occurrences (all)                                      | 3 / 149 (2.01%)<br>4    |  |  |
| Investigations<br>Weight decreased<br>subjects affected / exposed<br>occurrences (all)                     | 7 / 149 (4.70%)<br>7    |  |  |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all) | 18 / 149 (12.08%)<br>28 |  |  |
| Laceration<br>subjects affected / exposed<br>occurrences (all)                                             | 7 / 149 (4.70%)<br>7    |  |  |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                                              | 8 / 149 (5.37%)<br>10   |  |  |
| Skin abrasion<br>subjects affected / exposed<br>occurrences (all)                                          | 3 / 149 (2.01%)<br>5    |  |  |
| Nervous system disorders                                                                                   |                         |  |  |

|                                                                                                                   |                        |  |  |
|-------------------------------------------------------------------------------------------------------------------|------------------------|--|--|
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                                                     | 10 / 149 (6.71%)<br>11 |  |  |
| Cerebral microhaemorrhage<br>subjects affected / exposed<br>occurrences (all)                                     | 6 / 149 (4.03%)<br>7   |  |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                                                      | 3 / 149 (2.01%)<br>4   |  |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                       | 14 / 149 (9.40%)<br>23 |  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                                      | 8 / 149 (5.37%)<br>11  |  |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                                  | 5 / 149 (3.36%)<br>5   |  |  |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all)                | 6 / 149 (4.03%)<br>7   |  |  |
| Renal and urinary disorders<br>Urinary incontinence<br>subjects affected / exposed<br>occurrences (all)           | 8 / 149 (5.37%)<br>8   |  |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 8 / 149 (5.37%)<br>10  |  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                                                     | 8 / 149 (5.37%)<br>8   |  |  |
| Muscle spasms                                                                                                     |                        |  |  |

|                                         |                   |  |  |
|-----------------------------------------|-------------------|--|--|
| subjects affected / exposed             | 1 / 149 (0.67%)   |  |  |
| occurrences (all)                       | 2                 |  |  |
| Tendonitis                              |                   |  |  |
| subjects affected / exposed             | 0 / 149 (0.00%)   |  |  |
| occurrences (all)                       | 0                 |  |  |
| Infections and infestations             |                   |  |  |
| Urinary tract infection                 |                   |  |  |
| subjects affected / exposed             | 18 / 149 (12.08%) |  |  |
| occurrences (all)                       | 34                |  |  |
| Viral upper respiratory tract infection |                   |  |  |
| subjects affected / exposed             | 13 / 149 (8.72%)  |  |  |
| occurrences (all)                       | 13                |  |  |
| Upper respiratory tract infection       |                   |  |  |
| subjects affected / exposed             | 13 / 149 (8.72%)  |  |  |
| occurrences (all)                       | 15                |  |  |
| Bronchitis                              |                   |  |  |
| subjects affected / exposed             | 9 / 149 (6.04%)   |  |  |
| occurrences (all)                       | 9                 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 31 August 2012   | 1. Language was added to ensure subjects were followed for at least 90 days from their last dose of study drug, if they discontinue prematurely. 2. The Week 2 visit was removed in order to decrease visit burden for subjects and caregivers. 3. A baseline Columbia Suicide Severity Rating Scale (C-SSRS) measurement was added at Day 1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 23 August 2013   | 1. Included and excluded concomitant medications at screening and throughout the duration of the study were clarified. 2. Mini-Mental State Examination (MMSE) score required at enrollment was modified from greater than equal to 12 to greater than equal to 10. 3. Additional details regarding calculation and administration of the IV dose were provided.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 19 August 2014   | 1. Clinical study information on the closed studies NCT01397578 and NCT01343966 was provided. 2. Human clinical pharmacology and immunogenicity information was updated. 3. The SC dosing regimen was eliminated. Subjects previously receiving crenezumab 300 mg SC q2w now received crenezumab 15 mg/kg IV q4w, starting 2-4 weeks after the last SC dose. 4. An additional protocol-defined adverse event of special interest (AESI) was added to comply with internal Roche/Genentech pharmacovigilance policy, in line with Module VI of Guideline on good pharmacovigilance practices: suspected transmission of an infectious agent by the study drug, suggestive of a quality defect, with contamination of the concerned medicinal product. 5. An additional protocol-defined AESI was added to comply with internal Roche/Genentech pharmacovigilance policy to monitor for Hy's Law deviations of liver function. 6. An additional protocol-defined AESI for pneumonia was added. 7. Subjects were allowed to switch from a marketed treatment for Alzheimer's disease to a treatment at an equivalent dose if the marketed treatment for Alzheimer's disease is no longer available, either commercially or through the subject's insurance formulary. 8. Clarification was added for reporting persistent or recurrent adverse events.                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 28 August 2014   | 1. Visit at Weeks 23, 47, 71, and 93 that were inadvertently omitted from the Protocol's Study Flowcharts were included.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 22 November 2014 | 1. Clinical pharmacokinetics (PK) assessments were updated to include an elimination half-life estimate based on a population PK analysis of pooled PK data. 2. Based on the updated crenezumab half-life of 24.6 days, and updated Roche safety reporting policy, adverse events and pregnancy reporting periods were changed from 90 days to 8 weeks. It was also clarified that male subjects with partners with reproductive potential should use contraception for at least 8 weeks after the last dose of study drug. 3. The two safety follow-up visits have been consolidated into one safety follow-up visit occurring 8 weeks after the last administration of study drug. This change was made based on the safety profile to date of crenezumab and the above-mentioned updated Roche safety reporting policy. 4. The Open-Label Extension (OLE) treatment period was expanded by 52 weeks. Subjects could receive 13 additional doses (at Weeks 97, 101, 105, 109, 113, 117, 121, 125, 129, 133, 137, 141, and 145). For subjects who entered this additional OLE treatment period, safety follow-up visits occurred at Week 153. Subjects who had already discontinued treatment (either because of early treatment discontinuation or because they have already had their Week 93 dosing visit) could enter the additional OLE treatment period if they had not discontinued treatment for safety reasons. Subjects who have completed Study GN28525 or discontinued from Study GN28525 were not eligible to receive additional treatment. 5. Because the feeder studies NCT01343966 and NCT01397578 were completed and unblinded, it was specified that the Internal Safety Monitoring Committee would be disbanded, and periodic review of safety data would be conducted by the Sponsor project team. |

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Notes:

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported