



## Clinical trial results:

### A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, 2-Arm, Efficacy and Safety Study of NEOD001 Plus Standard of Care vs. Placebo Plus Standard of Care in Subjects with Light Chain (AL) Amyloidosis

#### Summary

|                          |                                  |
|--------------------------|----------------------------------|
| EudraCT number           | 2014-003865-11                   |
| Trial protocol           | DE AT ES BE NL FR GB GR PL DK IT |
| Global end of trial date | 08 June 2018                     |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 28 March 2019 |
| First version publication date | 28 March 2019 |

#### Trial information

##### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | NEOD001-CL002 |
|-----------------------|---------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02312206 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Prothena Therapeutics Limited, now merged into Prothena Biosciences Limited              |
| Sponsor organisation address | 77 Sir John Rogerson's Quay, Block C, Grand Canal Docklands, Dublin 2, Ireland, D02 T804 |
| Public contact               | Communications Office, Prothena Biosciences Inc, info@prothena.com                       |
| Scientific contact           | Clinical Trials Office, Prothena Biosciences Inc, info@prothena.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                       | 30 September 2018 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 08 June 2018      |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 08 June 2018      |
| Was the trial ended prematurely?                     | Yes               |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of NEOD001 plus standard of care (SOC) vs. placebo plus standard of care when administered intravenously in subjects with AL amyloidosis by assessing time to all- cause mortality or cardiac hospitalization

Protection of trial subjects:

This study was conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice, the principles of the Declaration of Helsinki, and with the laws of the countries in which the study was conducted. The Investigator had the ability to break the blind for a specific subject in the event of an immediate medical emergency, wherein knowledge of the subject's treatment (NEOD001 or placebo) needed to be known in order to provide adequate medical treatment. In these situations, the breaking of the blind was to be reported to the Sponsor or its designee within 24 hours. An independent DMC was in place to safeguard the interests of subjects in the study and to help ensure the integrity and credibility of the study.

Background therapy:

All subjects received concomitant standard of care chemotherapy, which must have included bortezomib administered subcutaneously on a weekly basis for the initial, first-line chemotherapy regimen. Subsequent chemotherapy regimens may have been prescribed as per standard of care at the Investigator's discretion. Antiviral prophylaxis was required.

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 27 April 2015 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Netherlands: 2     |
| Country: Number of subjects enrolled | Spain: 5           |
| Country: Number of subjects enrolled | United Kingdom: 14 |
| Country: Number of subjects enrolled | Austria: 6         |
| Country: Number of subjects enrolled | Belgium: 2         |
| Country: Number of subjects enrolled | Denmark: 1         |
| Country: Number of subjects enrolled | France: 22         |
| Country: Number of subjects enrolled | Germany: 22        |
| Country: Number of subjects enrolled | Greece: 15         |
| Country: Number of subjects enrolled | Australia: 12      |
| Country: Number of subjects enrolled | Canada: 8          |
| Country: Number of subjects enrolled | Israel: 6          |
| Country: Number of subjects enrolled | Italy: 3           |

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 142 |
| Worldwide total number of subjects   | 260                |
| EEA total number of subjects         | 92                 |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 139 |
| From 65 to 84 years                       | 117 |
| 85 years and over                         | 4   |

## Subject disposition

### Recruitment

Recruitment details:

A total of 260 subjects were enrolled in the study, 130 randomly assigned to receive NEOD001 and 130 randomly assigned to receive placebo.

### Pre-assignment

Screening details:

Screening evaluations and procedures were performed within 28 days prior to the first study drug administration on Month 1-Day 1. Individual test results that did not meet eligibility requirements could be repeated, with the exception of 6MWT; full rescreening was only allowed once per subject.

### Period 1

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

### Arms

|                              |                           |
|------------------------------|---------------------------|
| Are arms mutually exclusive? | Yes                       |
| <b>Arm title</b>             | NEOD001 24 mg/kg plus SOC |

Arm description:

NEOD001, 24 mg/kg IV every 4 weeks with concomitant standard of care chemotherapy, which must have included bortezomib administered subcutaneously on a weekly basis for the initial, first-line chemotherapy regimen. Subsequent chemotherapy regimens may have been prescribed as per standard of care at the Investigator's discretion.

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | NEOD001 24 mg/kg                 |
| Investigational medicinal product code |                                  |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

Study drug administered intravenously every 4 weeks for 12 months, starting at the Month 1-Day 1 Visit.

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Placebo plus SOC |
|------------------|------------------|

Arm description:

Placebo, 0.9% Saline IV every 4 weeks with concomitant standard of care chemotherapy, which must have included bortezomib administered subcutaneously on a weekly basis for the initial, first-line chemotherapy regimen. Subsequent chemotherapy regimens may have been prescribed as per standard of care at the Investigator's discretion.

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

Dosage and administration details:

Intravenous drip use (Noncurrent)

| <b>Number of subjects in period 1</b>                 | <b>NEOD001 24 mg/kg<br/>plus SOC</b> | <b>Placebo plus SOC</b> |
|---|--------------------------------------|-------------------------|
| Started   | 130                                  | 130                     |
| Informed Consent Obtained                             | 130                                  | 130                     |
| Not Completed   | 130                                  | 130                     |
| Completed   | 0                                    | 0                       |
| Not completed   | 130                                  | 130                     |
| Adverse event, serious fatal                          | 1                                    | -                       |
| Consent withdrawn by subject                          | 7                                    | 6                       |
| Physician decision                                    | 7                                    | 6                       |
| Disease progression                                   | 1                                    | -                       |
| Patient progression and institution<br>of new therapy | 1                                    | -                       |
| Subject missed three consecutive<br>treatment visits  | -                                    | 1                       |
| Adverse event, non-fatal                              | 2                                    | 6                       |
| Death   | 30                                   | 36                      |
| Study Terminated by Sponsor                           | 81                                   | 74                      |
| Patient transferred to hospice                        | -                                    | 1                       |

## Baseline characteristics

### Reporting groups

|   |                           |
|---|---------------------------|
| Reporting group title   | NEOD001 24 mg/kg plus SOC |
| Reporting group description:<br>NEOD001, 24 mg/kg IV every 4 weeks with concomitant standard of care chemotherapy, which must have included bortezomib administered subcutaneously on a weekly basis for the initial, first-line chemotherapy regimen. Subsequent chemotherapy regimens may have been prescribed as per standard of care at the Investigator's discretion.    |                           |
| Reporting group title   | Placebo plus SOC          |
| Reporting group description:<br>Placebo, 0.9% Saline IV every 4 weeks with concomitant standard of care chemotherapy, which must have included bortezomib administered subcutaneously on a weekly basis for the initial, first-line chemotherapy regimen. Subsequent chemotherapy regimens may have been prescribed as per standard of care at the Investigator's discretion. |                           |

| Reporting group values                | NEOD001 24 mg/kg plus SOC | Placebo plus SOC | Total |
|---------------------------------------|---------------------------|------------------|-------|
| Number of subjects                    | 130                       | 130              | 260   |
| Age categorical<br>Units: Subjects    |                           |                  |       |
| Adults (18-64 years)                  | 69                        | 70               | 139   |
| From 65-84 years                      | 61                        | 56               | 117   |
| 85 years and over                     | 0                         | 4                | 4     |
| Age continuous<br>Units: years        |                           |                  |       |
| arithmetic mean                       | 63.69                     | 63.24            |       |
| standard deviation                    | ± 9.478                   | ± 9.708          | -     |
| Gender categorical<br>Units: Subjects |                           |                  |       |
| Female                                | 48                        | 40               | 88    |
| Male                                  | 82                        | 90               | 172   |
| Race<br>Units: Subjects               |                           |                  |       |
| White                                 | 118                       | 120              | 238   |
| Black or African American             | 9                         | 3                | 12    |
| Not reported                          | 1                         | 5                | 6     |
| Asian                                 | 2                         | 2                | 4     |
| Ethnicity<br>Units: Subjects          |                           |                  |       |
| Hispanic or Latino                    | 2                         | 2                | 4     |
| Not Hispanic or Latino                | 116                       | 122              | 238   |
| Not reported                          | 12                        | 6                | 18    |

### Subject analysis sets

|  |   |
|--|---|
| Subject analysis set title   | NEOD001 24 mg/kg plus SOC (Safety Population) |
| Subject analysis set type  | Safety analysis                               |
| Subject analysis set description:<br>Safety population includes all subjects who received any amount of study drug |   |
| Subject analysis set title   | Placebo plus SOC (Safety Population)          |

|   |  |
|---|--|
| Subject analysis set type   | Safety analysis  |
| Subject analysis set description:   |  |
| Safety Population includes all subjects who received any amount of study drug   |  |
| Subject analysis set title  | NEOD001 24 mg/kg plus SOC (ITT Population)             |
| Subject analysis set type   | Intention-to-treat                                     |
| Subject analysis set description:   |  |
| ITT Population includes all randomized subjects who received any amount of study drug   |  |
| Subject analysis set title  | Placebo plus SOC (ITT Population)                      |
| Subject analysis set type   | Intention-to-treat                                     |
| Subject analysis set description:   |  |
| ITT Population includes all randomized subjects who received any amount of study drug   |  |
| Subject analysis set title  | NEOD001 24 mg/kg plus SOC (Renal Evaluable Population) |
| Subject analysis set type   | Sub-group analysis                                     |
| Subject analysis set description:   |  |
| Renal Evaluable Population includes all ITT subjects who had a baseline proteinuria >0.5 g/24 hours and at least one postbaseline assessment of 24 hour protein   |  |
| Subject analysis set title  | Placebo plus SOC (Renal Evaluable Population)          |
| Subject analysis set type   | Sub-group analysis                                     |
| Subject analysis set description:   |  |
| Renal Evaluable Population includes all ITT subjects who had a baseline proteinuria >0.5 g/24 hours and at least one postbaseline assessment of 24 hour protein   |  |
| Subject analysis set title  | NEOD001 24 mg/kg plus SOC (PN Evaluable Population)    |
| Subject analysis set type   | Sub-group analysis                                     |
| Subject analysis set description:   |  |
| Peripheral Neuropathy (PN) Evaluable Population includes all ITT subjects who had ascending sensorimotor neuropathy due to AL amyloidosis at screening and had a baseline NIS-LL total score $\geq 2$ and at least one postbaseline NIS-LL total score assessment |  |
| Subject analysis set title  | Placebo plus SOC (PN Evaluable Population)             |
| Subject analysis set type   | Sub-group analysis                                     |
| Subject analysis set description:   |  |
| Peripheral Neuropathy (PN) Evaluable Population includes all ITT subjects who had ascending sensorimotor neuropathy due to AL amyloidosis at screening and had a baseline NIS-LL total score $\geq 2$ and at least one postbaseline NIS-LL total score assessment |  |

| Reporting group values | NEOD001 24 mg/kg plus SOC (Safety Population) | Placebo plus SOC (Safety Population) | NEOD001 24 mg/kg plus SOC (ITT Population) |
|------------------------|---|--------------------------------------|--|
| Number of subjects     | 130   | 130                                  | 130  |
| Age categorical        |   |                                      |  |
| Units: Subjects        |   |                                      |  |
| Adults (18-64 years)   | 69  | 70                                   | 69   |
| From 65-84 years       | 61  | 56                                   | 61   |
| 85 years and over      | 0   | 4                                    | 0  |
| Age continuous         |   |                                      |  |
| Units: years           |   |                                      |  |
| arithmetic mean        | 63.69   | 63.24                                | 63.69                                      |
| standard deviation     | $\pm 9.478$                                   | $\pm 9.708$                          | $\pm 9.478$                                |
| Gender categorical     |   |                                      |  |
| Units: Subjects        |   |                                      |  |
| Female                 | 48  | 40                                   | 48   |
| Male                   | 82  | 90                                   | 82   |
| Race                   |   |                                      |  |
| Units: Subjects        |   |                                      |  |
| White                  | 118   | 120                                  | 118  |

|                              |     |     |     |
|------------------------------|-----|-----|-----|
| Black or African American    | 9   | 3   | 9   |
| Not reported                 | 1   | 5   | 1   |
| Asian                        | 2   | 2   | 2   |
| Ethnicity<br>Units: Subjects |     |     |     |
| Hispanic or Latino           | 2   | 2   | 2   |
| Not Hispanic or Latino       | 116 | 122 | 116 |
| Not reported                 | 12  | 6   | 12  |

| <b>Reporting group values</b>         | Placebo plus SOC<br>(ITT Population) | NEOD001 24 mg/kg<br>plus SOC (Renal<br>Evaluable<br>Population) | Placebo plus SOC<br>(Renal Evaluable<br>Population) |
|---------------------------------------|--------------------------------------|---|---|
| Number of subjects                    | 130                                  | 64  | 45  |
| Age categorical<br>Units: Subjects    |                                      |   |   |
| Adults (18-64 years)                  | 70                                   | 34  | 28  |
| From 65-84 years                      | 56                                   | 30  | 16  |
| 85 years and over                     | 4                                    | 0   | 1   |
| Age continuous<br>Units: years        |                                      |   |   |
| arithmetic mean                       | 63.24                                | 63.57   | 60.62   |
| standard deviation                    | ± 9.708                              | ± 8.256   | ± 10.100  |
| Gender categorical<br>Units: Subjects |                                      |   |   |
| Female                                | 40                                   | 18  | 13  |
| Male                                  | 90                                   | 46  | 32  |
| Race<br>Units: Subjects               |                                      |   |   |
| White                                 | 120                                  | 59  | 44  |
| Black or African American             | 3                                    | 2   | 0   |
| Not reported                          | 5                                    | 1   | 1   |
| Asian                                 | 2                                    | 2   | 0   |
| Ethnicity<br>Units: Subjects          |                                      |   |   |
| Hispanic or Latino                    | 2                                    | 2   | 0   |
| Not Hispanic or Latino                | 122                                  | 56  | 43  |
| Not reported                          | 6                                    | 6   | 2   |

| <b>Reporting group values</b>      | NEOD001 24 mg/kg<br>plus SOC (PN<br>Evaluable<br>Population) | Placebo plus SOC<br>(PN Evaluable<br>Population) |  |
|------------------------------------|--|--|--|
| Number of subjects                 | 15   | 14   |  |
| Age categorical<br>Units: Subjects |  |  |  |
| Adults (18-64 years)               | 8  | 7  |  |
| From 65-84 years                   | 7  | 7  |  |
| 85 years and over                  | 0  | 0  |  |
| Age continuous<br>Units: years     |  |  |  |
| arithmetic mean                    | 65.13  | 64.56  |  |
| standard deviation                 | ± 10.158   | ± 8.372  |  |



|                           |    |    |  |
|---------------------------|----|----|--|
| Gender categorical        |    |    |  |
| Units: Subjects           |    |    |  |
| Female                    | 2  | 3  |  |
| Male                      | 13 | 11 |  |
| Race                      |    |    |  |
| Units: Subjects           |    |    |  |
| White                     | 15 | 13 |  |
| Black or African American | 0  | 0  |  |
| Not reported              | 0  | 1  |  |
| Asian                     | 0  | 0  |  |
| Ethnicity                 |    |    |  |
| Units: Subjects           |    |    |  |
| Hispanic or Latino        | 0  | 0  |  |
| Not Hispanic or Latino    | 14 | 14 |  |
| Not reported              | 1  | 0  |  |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | NEOD001 24 mg/kg plus SOC                              |
| Reporting group description:<br>NEOD001, 24 mg/kg IV every 4 weeks with concomitant standard of care chemotherapy, which must have included bortezomib administered subcutaneously on a weekly basis for the initial, first-line chemotherapy regimen. Subsequent chemotherapy regimens may have been prescribed as per standard of care at the Investigator's discretion.    |  |
| Reporting group title   | Placebo plus SOC                                       |
| Reporting group description:<br>Placebo, 0.9% Saline IV every 4 weeks with concomitant standard of care chemotherapy, which must have included bortezomib administered subcutaneously on a weekly basis for the initial, first-line chemotherapy regimen. Subsequent chemotherapy regimens may have been prescribed as per standard of care at the Investigator's discretion. |  |
| Subject analysis set title  | NEOD001 24 mg/kg plus SOC (Safety Population)          |
| Subject analysis set type   | Safety analysis  |
| Subject analysis set description:<br>Safety population includes all subjects who received any amount of study drug  |  |
| Subject analysis set title  | Placebo plus SOC (Safety Population)                   |
| Subject analysis set type   | Safety analysis  |
| Subject analysis set description:<br>Safety Population includes all subjects who received any amount of study drug  |  |
| Subject analysis set title  | NEOD001 24 mg/kg plus SOC (ITT Population)             |
| Subject analysis set type   | Intention-to-treat                                     |
| Subject analysis set description:<br>ITT Population includes all randomized subjects who received any amount of study drug  |  |
| Subject analysis set title  | Placebo plus SOC (ITT Population)                      |
| Subject analysis set type   | Intention-to-treat                                     |
| Subject analysis set description:<br>ITT Population includes all randomized subjects who received any amount of study drug  |  |
| Subject analysis set title  | NEOD001 24 mg/kg plus SOC (Renal Evaluable Population) |
| Subject analysis set type   | Sub-group analysis                                     |
| Subject analysis set description:<br>Renal Evaluable Population includes all ITT subjects who had a baseline proteinuria >0.5 g/24 hours and at least one postbaseline assessment of 24 hour protein  |  |
| Subject analysis set title  | Placebo plus SOC (Renal Evaluable Population)          |
| Subject analysis set type   | Sub-group analysis                                     |
| Subject analysis set description:<br>Renal Evaluable Population includes all ITT subjects who had a baseline proteinuria >0.5 g/24 hours and at least one postbaseline assessment of 24 hour protein  |  |
| Subject analysis set title  | NEOD001 24 mg/kg plus SOC (PN Evaluable Population)    |
| Subject analysis set type   | Sub-group analysis                                     |
| Subject analysis set description:<br>Peripheral Neuropathy (PN) Evaluable Population includes all ITT subjects who had ascending sensorimotor neuropathy due to AL amyloidosis at screening and had a baseline NIS-LL total score >= 2 and at least one postbaseline NIS-LL total score assessment  |  |
| Subject analysis set title  | Placebo plus SOC (PN Evaluable Population)             |
| Subject analysis set type   | Sub-group analysis                                     |
| Subject analysis set description:<br>Peripheral Neuropathy (PN) Evaluable Population includes all ITT subjects who had ascending sensorimotor neuropathy due to AL amyloidosis at screening and had a baseline NIS-LL total score >= 2 and at least one postbaseline NIS-LL total score assessment  |  |

**Primary: Time to composite of all-cause mortality or cardiac hospitalization**

|   |   |
|---|---|
| End point title   | Time to composite of all-cause mortality or cardiac hospitalization |
| End point description:<br>Time to all-cause mortality death occurring after the first infusion of study drug or cardiac hospitalization as adjudicated by the CEC occurring at least 91 days after a first infusion of study drug through last subject last visit, whichever came first |   |
| End point type  | Primary   |
| End point timeframe:<br>Randomization until the date of death or cardiac hospitalization  |   |

| End point values                      | NEOD001 24 mg/kg plus SOC (ITT Population) | Placebo plus SOC (ITT Population) |  |  |
|---------------------------------------|--|-----------------------------------|--|--|
| Subject group type                    | Subject analysis set                       | Subject analysis set              |  |  |
| Number of subjects analysed           | 130  | 130                               |  |  |
| Units: Subjects                       |  |                                   |  |  |
| Died or cardiac hospitalization - Yes | 56   | 62                                |  |  |
| Died or cardiac hospitalization - No  | 74   | 68                                |  |  |

**Statistical analyses**

|   |  |
|---|--|
| Statistical analysis title  | Time to comp. all-cause mortality or cardiac hosp                              |
| Statistical analysis description:<br>Test to determine if the survival distribution of the time-to all-cause mortality or cardiac hospitalization is the same or different between placebo and NEOD001. |  |
| Comparison groups   | NEOD001 24 mg/kg plus SOC (ITT Population) v Placebo plus SOC (ITT Population) |
| Number of subjects included in analysis   | 260  |
| Analysis specification  | Pre-specified  |
| Analysis type   | superiority  |
| P-value   | = 0.33   |
| Method  | Logrank  |
| Parameter estimate  | Hazard ratio (HR)  |
| Point estimate  | 0.835  |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.5799   |
| upper limit   | 1.2011   |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Initiation of study drug through the last study visit or up to 30 days after last dose, whichever is later.

Adverse event reporting additional description:

AE that newly appears, increases in frequency, or worsens in severity following initiation of study drug and through the last study visit or up to 30 days after date of last dose, whichever is later.

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

### Dictionary used

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

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

### Reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | NEOD001 24 mg/kg plus SOC |
|-----------------------|---------------------------|

Reporting group description:

NEOD001 24 mg/kg IV every 4 weeks

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Placebo plus SOC |
|-----------------------|------------------|

Reporting group description:

Placebo, 0.9% Saline IV every 4 weeks

|                       |       |
|-----------------------|-------|
| Reporting group title | Total |
|-----------------------|-------|

Reporting group description:

Total NEOD001 + Placebo

| Serious adverse events  | NEOD001 24 mg/kg plus SOC | Placebo plus SOC  | Total              |
|---|---------------------------|-------------------|--------------------|
| Total subjects affected by serious adverse events                   |                           |                   |                    |
| subjects affected / exposed   | 88 / 130 (67.69%)         | 91 / 130 (70.00%) | 179 / 260 (68.85%) |
| number of deaths (all causes)                                       | 41                        | 42                | 83                 |
| number of deaths resulting from adverse events                      | 20                        | 32                | 52                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                           |                   |                    |
| Malignant melanoma  |                           |                   |                    |
| subjects affected / exposed   | 1 / 130 (0.77%)           | 0 / 130 (0.00%)   | 1 / 260 (0.38%)    |
| occurrences causally related to treatment / all                     | 0 / 2                     | 0 / 0             | 0 / 2              |
| deaths causally related to treatment / all                          | 0 / 0                     | 0 / 0             | 0 / 0              |
| Pericardial effusion malignant                                      |                           |                   |                    |
| subjects affected / exposed   | 1 / 130 (0.77%)           | 0 / 130 (0.00%)   | 1 / 260 (0.38%)    |
| occurrences causally related to treatment / all                     | 0 / 1                     | 0 / 0             | 0 / 1              |
| deaths causally related to treatment / all                          | 0 / 0                     | 0 / 0             | 0 / 0              |
| Prostate cancer   |                           |                   |                    |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                                   |                 |                 |                 |
| Deep vein thrombosis                                 |                 |                 |                 |
| subjects affected / exposed                          | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Embolism   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Haematoma  |                 |                 |                 |
| subjects affected / exposed                          | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypotension  |                 |                 |                 |
| subjects affected / exposed                          | 3 / 130 (2.31%) | 6 / 130 (4.62%) | 9 / 260 (3.46%) |
| occurrences causally related to treatment / all      | 0 / 5           | 0 / 6           | 0 / 11          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Orthostatic hypotension                              |                 |                 |                 |
| subjects affected / exposed                          | 2 / 130 (1.54%) | 3 / 130 (2.31%) | 5 / 260 (1.92%) |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 3           | 0 / 5           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral artery thrombosis                         |                 |                 |                 |
| subjects affected / exposed                          | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |
| Chest pain   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Death   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 2 / 130 (1.54%) | 3 / 260 (1.15%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 2           | 0 / 3           |
| General physical health deterioration           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Generalised oedema                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 3 / 130 (2.31%) | 3 / 260 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Malaise   |                 |                 |                 |
| subjects affected / exposed                     | 2 / 130 (1.54%) | 0 / 130 (0.00%) | 2 / 260 (0.77%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Multiple organ dysfunction syndrome             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| Oedema  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Oedema peripheral                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 2 / 130 (1.54%) | 3 / 260 (1.15%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyrexia   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sudden cardiac death                            |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 130 (0.77%) | 1 / 130 (0.77%) | 2 / 260 (0.77%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 2           |
| Sudden death                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 3 / 130 (2.31%) | 4 / 260 (1.54%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 3           | 0 / 4           |
| Immune system disorders                         |                 |                 |                 |
| Amyloidosis                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypersensitivity                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Chronic obstructive pulmonary disease           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dyspnoea  |                 |                 |                 |
| subjects affected / exposed                     | 3 / 130 (2.31%) | 0 / 130 (0.00%) | 3 / 260 (1.15%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoxia   |                 |                 |                 |
| subjects affected / exposed                     | 3 / 130 (2.31%) | 0 / 130 (0.00%) | 3 / 260 (1.15%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung disorder                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 3 / 130 (2.31%) | 4 / 260 (1.54%) |
| occurrences causally related to treatment / all | 0 / 2           | 2 / 3           | 2 / 5           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Lung infiltration                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 1           |
| Pleural effusion                                |                 |                 |                 |
| subjects affected / exposed                     | 2 / 130 (1.54%) | 6 / 130 (4.62%) | 8 / 260 (3.08%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 7           | 0 / 9           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia aspiration                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumothorax                                    |                 |                 |                 |
| subjects affected / exposed                     | 2 / 130 (1.54%) | 1 / 130 (0.77%) | 3 / 260 (1.15%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Productive cough                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary amyloidosis                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary embolism                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 1 / 130 (0.77%) | 2 / 260 (0.77%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary mass                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psychiatric disorders                           |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Confusional state                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Delirium  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mania   |                 |                 |                 |
| subjects affected / exposed                     | 2 / 130 (1.54%) | 0 / 130 (0.00%) | 2 / 260 (0.77%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Schizophrenia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Investigations                                  |                 |                 |                 |
| Blood creatinine increased                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| International normalised ratio increased        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial necrosis marker increased            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Neutrophil count decreased                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Troponin T increased                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| White blood cell count decreased                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Facial bones fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Femur fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fractured sacrum                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hip fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infusion related reaction                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lumbar vertebral fracture                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                  |
|---|-----------------|-----------------|------------------|
| Procedural haemorrhage                          |                 |                 |                  |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Toxicity to various agents                      |                 |                 |                  |
| subjects affected / exposed                     | 2 / 130 (1.54%) | 0 / 130 (0.00%) | 2 / 260 (0.77%)  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Cardiac disorders                               |                 |                 |                  |
| Acute myocardial infarction                     |                 |                 |                  |
| subjects affected / exposed                     | 3 / 130 (2.31%) | 1 / 130 (0.77%) | 4 / 260 (1.54%)  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Arrhythmia                                      |                 |                 |                  |
| subjects affected / exposed                     | 2 / 130 (1.54%) | 0 / 130 (0.00%) | 2 / 260 (0.77%)  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           | 0 / 2            |
| Atrial fibrillation                             |                 |                 |                  |
| subjects affected / exposed                     | 6 / 130 (4.62%) | 6 / 130 (4.62%) | 12 / 260 (4.62%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 7           | 0 / 13           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Atrial flutter                                  |                 |                 |                  |
| subjects affected / exposed                     | 2 / 130 (1.54%) | 0 / 130 (0.00%) | 2 / 260 (0.77%)  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Atrioventricular block                          |                 |                 |                  |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Atrioventricular block complete                 |                 |                 |                  |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Bradycardia                                     |                 |                 |                  |

|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed                     | 1 / 130 (0.77%)   | 0 / 130 (0.00%)   | 1 / 260 (0.38%)   |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Cardiac amyloidosis                             |                   |                   |                   |
| subjects affected / exposed                     | 1 / 130 (0.77%)   | 1 / 130 (0.77%)   | 2 / 260 (0.77%)   |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1             | 0 / 2             |
| Cardiac arrest                                  |                   |                   |                   |
| subjects affected / exposed                     | 9 / 130 (6.92%)   | 10 / 130 (7.69%)  | 19 / 260 (7.31%)  |
| occurrences causally related to treatment / all | 0 / 10            | 0 / 13            | 0 / 23            |
| deaths causally related to treatment / all      | 0 / 5             | 0 / 6             | 0 / 11            |
| Cardiac failure                                 |                   |                   |                   |
| subjects affected / exposed                     | 17 / 130 (13.08%) | 28 / 130 (21.54%) | 45 / 260 (17.31%) |
| occurrences causally related to treatment / all | 0 / 35            | 0 / 35            | 0 / 70            |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 5             | 0 / 6             |
| Cardiac failure acute                           |                   |                   |                   |
| subjects affected / exposed                     | 6 / 130 (4.62%)   | 5 / 130 (3.85%)   | 11 / 260 (4.23%)  |
| occurrences causally related to treatment / all | 0 / 7             | 0 / 7             | 0 / 14            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             | 0 / 1             |
| Cardiac failure chronic                         |                   |                   |                   |
| subjects affected / exposed                     | 0 / 130 (0.00%)   | 1 / 130 (0.77%)   | 1 / 260 (0.38%)   |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Cardiac failure congestive                      |                   |                   |                   |
| subjects affected / exposed                     | 17 / 130 (13.08%) | 9 / 130 (6.92%)   | 26 / 260 (10.00%) |
| occurrences causally related to treatment / all | 0 / 19            | 0 / 11            | 0 / 30            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             | 0 / 1             |
| Cardiac ventricular thrombosis                  |                   |                   |                   |
| subjects affected / exposed                     | 1 / 130 (0.77%)   | 0 / 130 (0.00%)   | 1 / 260 (0.38%)   |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Cardio-respiratory arrest                       |                   |                   |                   |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| Cardiogenic shock                               |                 |                 |                 |
| subjects affected / exposed                     | 3 / 130 (2.31%) | 1 / 130 (0.77%) | 4 / 260 (1.54%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 2           |
| Cardiopulmonary failure                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Conduction disorder                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| Coronary artery disease                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Left ventricular dysfunction                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pericardial effusion                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sinus bradycardia                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sinus tachycardia                               |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Supraventricular tachycardia                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ventricular arrhythmia                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ventricular fibrillation                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| Ventricular tachycardia                         |                 |                 |                 |
| subjects affected / exposed                     | 2 / 130 (1.54%) | 5 / 130 (3.85%) | 7 / 260 (2.69%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 5           | 0 / 7           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Brain injury                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebrovascular accident                        |                 |                 |                 |
| subjects affected / exposed                     | 2 / 130 (1.54%) | 0 / 130 (0.00%) | 2 / 260 (0.77%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dizziness                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Encephalopathy                                  |                 |                 |                 |

|   |                  |                 |                  |
|---|------------------|-----------------|------------------|
| subjects affected / exposed                     | 1 / 130 (0.77%)  | 0 / 130 (0.00%) | 1 / 260 (0.38%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Facial paralysis                                |                  |                 |                  |
| subjects affected / exposed                     | 1 / 130 (0.77%)  | 0 / 130 (0.00%) | 1 / 260 (0.38%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Haemorrhagic stroke                             |                  |                 |                  |
| subjects affected / exposed                     | 1 / 130 (0.77%)  | 0 / 130 (0.00%) | 1 / 260 (0.38%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Ischaemic stroke                                |                  |                 |                  |
| subjects affected / exposed                     | 0 / 130 (0.00%)  | 1 / 130 (0.77%) | 1 / 260 (0.38%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Partial seizures                                |                  |                 |                  |
| subjects affected / exposed                     | 0 / 130 (0.00%)  | 1 / 130 (0.77%) | 1 / 260 (0.38%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Seizure   |                  |                 |                  |
| subjects affected / exposed                     | 0 / 130 (0.00%)  | 2 / 130 (1.54%) | 2 / 260 (0.77%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2           | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Syncope   |                  |                 |                  |
| subjects affected / exposed                     | 11 / 130 (8.46%) | 7 / 130 (5.38%) | 18 / 260 (6.92%) |
| occurrences causally related to treatment / all | 0 / 12           | 0 / 9           | 0 / 21           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           | 0 / 1            |
| Blood and lymphatic system disorders            |                  |                 |                  |
| Anaemia   |                  |                 |                  |
| subjects affected / exposed                     | 1 / 130 (0.77%)  | 2 / 130 (1.54%) | 3 / 260 (1.15%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2           | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Coagulation factor deficiency                   |                  |                 |                  |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lymphopenia                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Thrombocytopenia                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 2 / 130 (1.54%) | 3 / 260 (1.15%) |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 2           | 1 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Abdominal pain                                  |                 |                 |                 |
| subjects affected / exposed                     | 4 / 130 (3.08%) | 0 / 130 (0.00%) | 4 / 260 (1.54%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ascites   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colitis   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 1 / 130 (0.77%) | 2 / 260 (0.77%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colitis ulcerative                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colonic pseudo-obstruction                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Constipation                                    |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 130 (0.00%) | 3 / 130 (2.31%) | 3 / 260 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diarrhoea                                       |                 |                 |                 |
| subjects affected / exposed                     | 3 / 130 (2.31%) | 1 / 130 (0.77%) | 4 / 260 (1.54%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diverticular perforation                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal haemorrhage                    |                 |                 |                 |
| subjects affected / exposed                     | 3 / 130 (2.31%) | 1 / 130 (0.77%) | 4 / 260 (1.54%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haematochezia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhoids                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ileus   |                 |                 |                 |
| subjects affected / exposed                     | 3 / 130 (2.31%) | 1 / 130 (0.77%) | 4 / 260 (1.54%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Incarcerated umbilical hernia                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mesenteric artery thrombosis                    |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nausea  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Oesophagitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pancreatitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rectal haemorrhage                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Small intestinal obstruction                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vomiting  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 130 (1.54%) | 2 / 130 (1.54%) | 4 / 260 (1.54%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Cholecystitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 1 / 130 (0.77%) | 2 / 260 (0.77%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhagic hepatic cyst                       |                 |                 |                 |

|   |                 |                 |                  |
|---|-----------------|-----------------|------------------|
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Hepatic failure                                 |                 |                 |                  |
| subjects affected / exposed                     | 2 / 130 (1.54%) | 0 / 130 (0.00%) | 2 / 260 (0.77%)  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 1            |
| Hepatic haematoma                               |                 |                 |                  |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Hepatosplenomegaly                              |                 |                 |                  |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Skin and subcutaneous tissue disorders          |                 |                 |                  |
| Rash maculo-papular                             |                 |                 |                  |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Renal and urinary disorders                     |                 |                 |                  |
| Acute kidney injury                             |                 |                 |                  |
| subjects affected / exposed                     | 7 / 130 (5.38%) | 9 / 130 (6.92%) | 16 / 260 (6.15%) |
| occurrences causally related to treatment / all | 0 / 8           | 0 / 10          | 0 / 18           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Anuria  |                 |                 |                  |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Chronic kidney disease                          |                 |                 |                  |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 1 / 130 (0.77%) | 2 / 260 (0.77%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Dysuria   |                 |                 |                  |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haematuria                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 1 / 130 (0.77%) | 2 / 260 (0.77%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hydronephrosis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nephrolithiasis                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nephrotic syndrome                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal failure                                   |                 |                 |                 |
| subjects affected / exposed                     | 2 / 130 (1.54%) | 4 / 130 (3.08%) | 6 / 260 (2.31%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 4           | 0 / 6           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal impairment                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 1 / 130 (0.77%) | 2 / 260 (0.77%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| Urinary retention                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Muscle spasms                                   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pain in extremity                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Polymyalgia rheumatica                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| Abdominal abscess                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bacteraemia                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bacterial infection                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bronchiolitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bronchitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 3 / 130 (2.31%) | 3 / 260 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cellulitis                                      |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastroenteritis                                 |                 |                 |                 |
| subjects affected / exposed                     | 3 / 130 (2.31%) | 1 / 130 (0.77%) | 4 / 260 (1.54%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Herpes zoster                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infection                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Influenza                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 2 / 130 (1.54%) | 2 / 260 (0.77%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| Injection site cellulitis                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lower respiratory tract infection               |                 |                 |                 |
| subjects affected / exposed                     | 3 / 130 (2.31%) | 0 / 130 (0.00%) | 3 / 260 (1.15%) |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           | 1 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung infection                                  |                 |                 |                 |
| subjects affected / exposed                     | 3 / 130 (2.31%) | 4 / 130 (3.08%) | 7 / 260 (2.69%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 4           | 0 / 7           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Parainfluenzae virus infection                  |                 |                 |                 |

|   |                  |                 |                  |
|---|------------------|-----------------|------------------|
| subjects affected / exposed                     | 1 / 130 (0.77%)  | 0 / 130 (0.00%) | 1 / 260 (0.38%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Pasteurella infection                           |                  |                 |                  |
| subjects affected / exposed                     | 0 / 130 (0.00%)  | 1 / 130 (0.77%) | 1 / 260 (0.38%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Peritonitis bacterial                           |                  |                 |                  |
| subjects affected / exposed                     | 0 / 130 (0.00%)  | 1 / 130 (0.77%) | 1 / 260 (0.38%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 5           | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Pneumococcal sepsis                             |                  |                 |                  |
| subjects affected / exposed                     | 0 / 130 (0.00%)  | 1 / 130 (0.77%) | 1 / 260 (0.38%)  |
| 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                                       |                  |                 |                  |
| subjects affected / exposed                     | 11 / 130 (8.46%) | 9 / 130 (6.92%) | 20 / 260 (7.69%) |
| occurrences causally related to treatment / all | 0 / 16           | 0 / 10          | 0 / 26           |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1           | 0 / 2            |
| Pneumonia viral                                 |                  |                 |                  |
| subjects affected / exposed                     | 1 / 130 (0.77%)  | 0 / 130 (0.00%) | 1 / 260 (0.38%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Pyelonephritis                                  |                  |                 |                  |
| subjects affected / exposed                     | 1 / 130 (0.77%)  | 0 / 130 (0.00%) | 1 / 260 (0.38%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Respiratory syncytial virus infection           |                  |                 |                  |
| subjects affected / exposed                     | 0 / 130 (0.00%)  | 1 / 130 (0.77%) | 1 / 260 (0.38%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Sepsis  |                  |                 |                  |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 3 / 130 (2.31%) | 2 / 130 (1.54%) | 5 / 260 (1.92%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           | 0 / 6           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| Septic shock                                    |                 |                 |                 |
| subjects affected / exposed                     | 4 / 130 (3.08%) | 1 / 130 (0.77%) | 5 / 260 (1.92%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 4           | 0 / 1           | 0 / 5           |
| Soft tissue infection                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Upper respiratory tract infection               |                 |                 |                 |
| subjects affected / exposed                     | 4 / 130 (3.08%) | 0 / 130 (0.00%) | 4 / 260 (1.54%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 0           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 2 / 130 (1.54%) | 0 / 130 (0.00%) | 2 / 260 (0.77%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urosepsis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Viral infection                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 2 / 130 (1.54%) | 2 / 260 (0.77%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Cell death                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dehydration                                     |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 130 (0.00%) | 3 / 130 (2.31%) | 3 / 260 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Failure to thrive                               |                 |                 |                 |
| subjects affected / exposed                     | 2 / 130 (1.54%) | 0 / 130 (0.00%) | 2 / 260 (0.77%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fluid overload                                  |                 |                 |                 |
| subjects affected / exposed                     | 5 / 130 (3.85%) | 4 / 130 (3.08%) | 9 / 260 (3.46%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 5           | 0 / 10          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fluid retention                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 130 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperkalaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 2 / 130 (1.54%) | 1 / 130 (0.77%) | 3 / 260 (1.15%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypervolaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 2 / 130 (1.54%) | 1 / 130 (0.77%) | 3 / 260 (1.15%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypokalaemia                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 130 (0.77%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyponatraemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 5 / 130 (3.85%) | 3 / 130 (2.31%) | 8 / 260 (3.08%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 3           | 0 / 9           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypovolaemia                                    |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 130 (0.77%) | 1 / 130 (0.77%) | 2 / 260 (0.77%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

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

| <b>Non-serious adverse events</b>                     | NEOD001 24 mg/kg<br>plus SOC | Placebo plus SOC   | Total              |
|---|------------------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events |                              |                    |                    |
| subjects affected / exposed                           | 122 / 130 (93.85%)           | 123 / 130 (94.62%) | 245 / 260 (94.23%) |
| Vascular disorders                                    |                              |                    |                    |
| Hypotension   |                              |                    |                    |
| subjects affected / exposed                           | 20 / 130 (15.38%)            | 29 / 130 (22.31%)  | 49 / 260 (18.85%)  |
| occurrences (all)                                     | 29                           | 54                 | 83                 |
| Orthostatic hypotension                               |                              |                    |                    |
| subjects affected / exposed                           | 9 / 130 (6.92%)              | 13 / 130 (10.00%)  | 22 / 260 (8.46%)   |
| occurrences (all)                                     | 13                           | 13                 | 26                 |
| General disorders and administration site conditions  |                              |                    |                    |
| Asthenia  |                              |                    |                    |
| subjects affected / exposed                           | 9 / 130 (6.92%)              | 9 / 130 (6.92%)    | 18 / 260 (6.92%)   |
| occurrences (all)                                     | 18                           | 10                 | 28                 |
| Chills  |                              |                    |                    |
| subjects affected / exposed                           | 9 / 130 (6.92%)              | 4 / 130 (3.08%)    | 13 / 260 (5.00%)   |
| occurrences (all)                                     | 11                           | 4                  | 15                 |
| Fatigue   |                              |                    |                    |
| subjects affected / exposed                           | 57 / 130 (43.85%)            | 52 / 130 (40.00%)  | 109 / 260 (41.92%) |
| occurrences (all)                                     | 125                          | 90                 | 215                |
| Oedema peripheral                                     |                              |                    |                    |
| subjects affected / exposed                           | 55 / 130 (42.31%)            | 56 / 130 (43.08%)  | 111 / 260 (42.69%) |
| occurrences (all)                                     | 112                          | 88                 | 200                |
| Pyrexia   |                              |                    |                    |
| subjects affected / exposed                           | 12 / 130 (9.23%)             | 11 / 130 (8.46%)   | 23 / 260 (8.85%)   |
| occurrences (all)                                     | 18                           | 13                 | 31                 |
| Respiratory, thoracic and mediastinal disorders       |                              |                    |                    |
| Cough   |                              |                    |                    |

|                                      |                   |                   |                   |
|--------------------------------------|-------------------|-------------------|-------------------|
| subjects affected / exposed          | 31 / 130 (23.85%) | 27 / 130 (20.77%) | 58 / 260 (22.31%) |
| occurrences (all)                    | 46                | 33                | 79                |
| Dyspnoea                             |                   |                   |                   |
| subjects affected / exposed          | 38 / 130 (29.23%) | 40 / 130 (30.77%) | 78 / 260 (30.00%) |
| occurrences (all)                    | 63                | 68                | 131               |
| Dyspnoea exertional                  |                   |                   |                   |
| subjects affected / exposed          | 11 / 130 (8.46%)  | 7 / 130 (5.38%)   | 18 / 260 (6.92%)  |
| occurrences (all)                    | 13                | 13                | 26                |
| Epistaxis                            |                   |                   |                   |
| subjects affected / exposed          | 8 / 130 (6.15%)   | 7 / 130 (5.38%)   | 15 / 260 (5.77%)  |
| occurrences (all)                    | 9                 | 7                 | 16                |
| Pleural effusion                     |                   |                   |                   |
| subjects affected / exposed          | 8 / 130 (6.15%)   | 13 / 130 (10.00%) | 21 / 260 (8.08%)  |
| occurrences (all)                    | 10                | 15                | 25                |
| Psychiatric disorders                |                   |                   |                   |
| Anxiety                              |                   |                   |                   |
| subjects affected / exposed          | 11 / 130 (8.46%)  | 3 / 130 (2.31%)   | 14 / 260 (5.38%)  |
| occurrences (all)                    | 11                | 3                 | 14                |
| Depression                           |                   |                   |                   |
| subjects affected / exposed          | 11 / 130 (8.46%)  | 7 / 130 (5.38%)   | 18 / 260 (6.92%)  |
| occurrences (all)                    | 13                | 8                 | 21                |
| Insomnia                             |                   |                   |                   |
| subjects affected / exposed          | 39 / 130 (30.00%) | 30 / 130 (23.08%) | 69 / 260 (26.54%) |
| occurrences (all)                    | 41                | 35                | 76                |
| Investigations                       |                   |                   |                   |
| Alanine aminotransferase increased   |                   |                   |                   |
| subjects affected / exposed          | 5 / 130 (3.85%)   | 8 / 130 (6.15%)   | 13 / 260 (5.00%)  |
| occurrences (all)                    | 5                 | 10                | 15                |
| Aspartate aminotransferase increased |                   |                   |                   |
| subjects affected / exposed          | 11 / 130 (8.46%)  | 8 / 130 (6.15%)   | 19 / 260 (7.31%)  |
| occurrences (all)                    | 13                | 14                | 27                |
| Blood alkaline phosphatase increased |                   |                   |                   |
| subjects affected / exposed          | 12 / 130 (9.23%)  | 5 / 130 (3.85%)   | 17 / 260 (6.54%)  |
| occurrences (all)                    | 36                | 7                 | 43                |
| Blood creatinine increased           |                   |                   |                   |

|  |                         |                         |                         |
|--|-------------------------|-------------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)                             | 22 / 130 (16.92%)<br>55 | 11 / 130 (8.46%)<br>21  | 33 / 260 (12.69%)<br>76 |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all) | 4 / 130 (3.08%)<br>11   | 10 / 130 (7.69%)<br>20  | 14 / 260 (5.38%)<br>31  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)         | 19 / 130 (14.62%)<br>25 | 16 / 130 (12.31%)<br>23 | 35 / 260 (13.46%)<br>48 |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)         | 6 / 130 (4.62%)<br>12   | 11 / 130 (8.46%)<br>12  | 17 / 260 (6.54%)<br>24  |
| Injury, poisoning and procedural complications                               |                         |                         |                         |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                | 8 / 130 (6.15%)<br>10   | 10 / 130 (7.69%)<br>12  | 18 / 260 (6.92%)<br>22  |
| Fall<br>subjects affected / exposed<br>occurrences (all)                     | 14 / 130 (10.77%)<br>18 | 10 / 130 (7.69%)<br>14  | 24 / 260 (9.23%)<br>32  |
| Cardiac disorders  |                         |                         |                         |
| Atrial fibrillation<br>subjects affected / exposed<br>occurrences (all)      | 8 / 130 (6.15%)<br>10   | 10 / 130 (7.69%)<br>15  | 18 / 260 (6.92%)<br>25  |
| Cardiac failure<br>subjects affected / exposed<br>occurrences (all)          | 9 / 130 (6.92%)<br>13   | 6 / 130 (4.62%)<br>6    | 15 / 260 (5.77%)<br>19  |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)             | 3 / 130 (2.31%)<br>3    | 11 / 130 (8.46%)<br>15  | 14 / 260 (5.38%)<br>18  |
| Nervous system disorders   |                         |                         |                         |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                | 25 / 130 (19.23%)<br>35 | 38 / 130 (29.23%)<br>54 | 63 / 260 (24.23%)<br>89 |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)                | 10 / 130 (7.69%)<br>12  | 12 / 130 (9.23%)<br>12  | 22 / 260 (8.46%)<br>24  |
| Headache   |                         |                         |                         |

|                                      |                   |                   |                   |
|--------------------------------------|-------------------|-------------------|-------------------|
| subjects affected / exposed          | 17 / 130 (13.08%) | 16 / 130 (12.31%) | 33 / 260 (12.69%) |
| occurrences (all)                    | 20                | 21                | 41                |
| Neuropathy peripheral                |                   |                   |                   |
| subjects affected / exposed          | 30 / 130 (23.08%) | 17 / 130 (13.08%) | 47 / 260 (18.08%) |
| occurrences (all)                    | 43                | 27                | 70                |
| Paraesthesia                         |                   |                   |                   |
| subjects affected / exposed          | 10 / 130 (7.69%)  | 13 / 130 (10.00%) | 23 / 260 (8.85%)  |
| occurrences (all)                    | 14                | 18                | 32                |
| Peripheral sensory neuropathy        |                   |                   |                   |
| subjects affected / exposed          | 14 / 130 (10.77%) | 13 / 130 (10.00%) | 27 / 260 (10.38%) |
| occurrences (all)                    | 23                | 23                | 46                |
| Syncope                              |                   |                   |                   |
| subjects affected / exposed          | 7 / 130 (5.38%)   | 11 / 130 (8.46%)  | 18 / 260 (6.92%)  |
| occurrences (all)                    | 10                | 17                | 27                |
| Blood and lymphatic system disorders |                   |                   |                   |
| Anaemia                              |                   |                   |                   |
| subjects affected / exposed          | 21 / 130 (16.15%) | 27 / 130 (20.77%) | 48 / 260 (18.46%) |
| occurrences (all)                    | 43                | 67                | 110               |
| Lymphopenia                          |                   |                   |                   |
| subjects affected / exposed          | 6 / 130 (4.62%)   | 7 / 130 (5.38%)   | 13 / 260 (5.00%)  |
| occurrences (all)                    | 19                | 18                | 37                |
| Thrombocytopenia                     |                   |                   |                   |
| subjects affected / exposed          | 10 / 130 (7.69%)  | 9 / 130 (6.92%)   | 19 / 260 (7.31%)  |
| occurrences (all)                    | 17                | 19                | 36                |
| Gastrointestinal disorders           |                   |                   |                   |
| Abdominal distension                 |                   |                   |                   |
| subjects affected / exposed          | 15 / 130 (11.54%) | 15 / 130 (11.54%) | 30 / 260 (11.54%) |
| occurrences (all)                    | 23                | 17                | 40                |
| Abdominal pain                       |                   |                   |                   |
| subjects affected / exposed          | 13 / 130 (10.00%) | 15 / 130 (11.54%) | 28 / 260 (10.77%) |
| occurrences (all)                    | 19                | 16                | 35                |
| Abdominal pain upper                 |                   |                   |                   |
| subjects affected / exposed          | 6 / 130 (4.62%)   | 8 / 130 (6.15%)   | 14 / 260 (5.38%)  |
| occurrences (all)                    | 6                 | 8                 | 14                |
| Constipation                         |                   |                   |                   |

|  |                          |                         |                           |
|--|--------------------------|-------------------------|---------------------------|
| subjects affected / exposed<br>occurrences (all)                           | 55 / 130 (42.31%)<br>75  | 55 / 130 (42.31%)<br>82 | 110 / 260 (42.31%)<br>157 |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)              | 51 / 130 (39.23%)<br>110 | 54 / 130 (41.54%)<br>82 | 105 / 260 (40.38%)<br>192 |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                 | 56 / 130 (43.08%)<br>86  | 43 / 130 (33.08%)<br>71 | 99 / 260 (38.08%)<br>157  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)             | 7 / 130 (5.38%)<br>7     | 8 / 130 (6.15%)<br>9    | 15 / 260 (5.77%)<br>16    |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)               | 27 / 130 (20.77%)<br>42  | 20 / 130 (15.38%)<br>32 | 47 / 260 (18.08%)<br>74   |
| Skin and subcutaneous tissue disorders                                     |                          |                         |                           |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)               | 7 / 130 (5.38%)<br>7     | 7 / 130 (5.38%)<br>7    | 14 / 260 (5.38%)<br>14    |
| Ecchymosis<br>subjects affected / exposed<br>occurrences (all)             | 7 / 130 (5.38%)<br>7     | 8 / 130 (6.15%)<br>8    | 15 / 260 (5.77%)<br>15    |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)               | 14 / 130 (10.77%)<br>19  | 12 / 130 (9.23%)<br>14  | 26 / 260 (10.00%)<br>33   |
| Rash<br>subjects affected / exposed<br>occurrences (all)                   | 15 / 130 (11.54%)<br>16  | 18 / 130 (13.85%)<br>24 | 33 / 260 (12.69%)<br>40   |
| Renal and urinary disorders  |                          |                         |                           |
| Acute kidney injury<br>subjects affected / exposed<br>occurrences (all)    | 9 / 130 (6.92%)<br>16    | 4 / 130 (3.08%)<br>9    | 13 / 260 (5.00%)<br>25    |
| Chronic kidney disease<br>subjects affected / exposed<br>occurrences (all) | 7 / 130 (5.38%)<br>17    | 6 / 130 (4.62%)<br>10   | 13 / 260 (5.00%)<br>27    |
| Musculoskeletal and connective tissue disorders                            |                          |                         |                           |

|                                    |                   |                   |                   |
|------------------------------------|-------------------|-------------------|-------------------|
| Arthralgia                         |                   |                   |                   |
| subjects affected / exposed        | 12 / 130 (9.23%)  | 6 / 130 (4.62%)   | 18 / 260 (6.92%)  |
| occurrences (all)                  | 18                | 7                 | 25                |
| Back pain                          |                   |                   |                   |
| subjects affected / exposed        | 15 / 130 (11.54%) | 12 / 130 (9.23%)  | 27 / 260 (10.38%) |
| occurrences (all)                  | 17                | 12                | 29                |
| Muscle spasms                      |                   |                   |                   |
| subjects affected / exposed        | 15 / 130 (11.54%) | 7 / 130 (5.38%)   | 22 / 260 (8.46%)  |
| occurrences (all)                  | 17                | 8                 | 25                |
| Muscular weakness                  |                   |                   |                   |
| subjects affected / exposed        | 9 / 130 (6.92%)   | 5 / 130 (3.85%)   | 14 / 260 (5.38%)  |
| occurrences (all)                  | 12                | 9                 | 21                |
| Pain in extremity                  |                   |                   |                   |
| subjects affected / exposed        | 14 / 130 (10.77%) | 8 / 130 (6.15%)   | 22 / 260 (8.46%)  |
| occurrences (all)                  | 16                | 11                | 27                |
| Infections and infestations        |                   |                   |                   |
| Nasopharyngitis                    |                   |                   |                   |
| subjects affected / exposed        | 8 / 130 (6.15%)   | 10 / 130 (7.69%)  | 18 / 260 (6.92%)  |
| occurrences (all)                  | 9                 | 14                | 23                |
| Pneumonia                          |                   |                   |                   |
| subjects affected / exposed        | 8 / 130 (6.15%)   | 8 / 130 (6.15%)   | 16 / 260 (6.15%)  |
| occurrences (all)                  | 11                | 8                 | 19                |
| Upper respiratory tract infection  |                   |                   |                   |
| subjects affected / exposed        | 23 / 130 (17.69%) | 25 / 130 (19.23%) | 48 / 260 (18.46%) |
| occurrences (all)                  | 28                | 34                | 62                |
| Urinary tract infection            |                   |                   |                   |
| subjects affected / exposed        | 14 / 130 (10.77%) | 6 / 130 (4.62%)   | 20 / 260 (7.69%)  |
| occurrences (all)                  | 17                | 8                 | 25                |
| Metabolism and nutrition disorders |                   |                   |                   |
| Decreased appetite                 |                   |                   |                   |
| subjects affected / exposed        | 27 / 130 (20.77%) | 20 / 130 (15.38%) | 47 / 260 (18.08%) |
| occurrences (all)                  | 34                | 28                | 62                |
| Hyperglycaemia                     |                   |                   |                   |
| subjects affected / exposed        | 8 / 130 (6.15%)   | 8 / 130 (6.15%)   | 16 / 260 (6.15%)  |
| occurrences (all)                  | 47                | 11                | 58                |
| Hyperkalaemia                      |                   |                   |                   |

|                             |                   |                   |                   |
|-----------------------------|-------------------|-------------------|-------------------|
| subjects affected / exposed | 9 / 130 (6.92%)   | 8 / 130 (6.15%)   | 17 / 260 (6.54%)  |
| occurrences (all)           | 15                | 16                | 31                |
| Hyperuricaemia              |                   |                   |                   |
| subjects affected / exposed | 9 / 130 (6.92%)   | 13 / 130 (10.00%) | 22 / 260 (8.46%)  |
| occurrences (all)           | 18                | 17                | 35                |
| Hypoalbuminaemia            |                   |                   |                   |
| subjects affected / exposed | 7 / 130 (5.38%)   | 6 / 130 (4.62%)   | 13 / 260 (5.00%)  |
| occurrences (all)           | 24                | 11                | 35                |
| Hypokalaemia                |                   |                   |                   |
| subjects affected / exposed | 24 / 130 (18.46%) | 26 / 130 (20.00%) | 50 / 260 (19.23%) |
| occurrences (all)           | 72                | 47                | 119               |
| Hyponatraemia               |                   |                   |                   |
| subjects affected / exposed | 16 / 130 (12.31%) | 17 / 130 (13.08%) | 33 / 260 (12.69%) |
| occurrences (all)           | 46                | 42                | 88                |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 28 April 2016    | This global protocol amendment incorporates changes that were made during several country-specific amendments, which were issued between the finalization of Amendment 1 and this global Amendment 2.   |
| 06 November 2017 | Overview of Major/Substantial Changes:<br>Aligned with updated case report form and statistical analysis plan<br>Removed requirement for monthly collection of additional coagulation indices<br>Removed sample collection for quantitative/renal biomarkers<br>Allowed postbaseline 6MWT to be administered on the same calendar day that study drug is administered<br>Increased the number of subjects<br>Clarified timing of serious adverse event collection |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported