



## Clinical trial results:

**A placebo-controlled, double-blind, randomized trial to compare the effect of different doses of inclisiran given as single or multiple subcutaneous injections in subjects with high cardiovascular risk and elevated LDL-C.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-003772-74 |
| Trial protocol           | GB DE NL       |
| Global end of trial date | 07 June 2017   |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 20 February 2019 |
| First version publication date | 20 February 2019 |

### Trial information

#### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | MDCO-PCS-15-01 |
|-----------------------|----------------|

#### Additional study identifiers

|                                    |                     |
|------------------------------------|---------------------|
| ISRCTN number                      | -                   |
| ClinicalTrials.gov id (NCT number) | NCT02597127         |
| WHO universal trial number (UTN)   | -                   |
| Other trial identifiers            | Trial Name: ORION-1 |

Notes:

### Sponsors

|                              |                                                                                                      |
|------------------------------|------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | The Medicines Company                                                                                |
| Sponsor organisation address | 8 Sylvan Way, Parsippany, United States, NJ 07054                                                    |
| Public contact               | Global Health Science Center, The Medicines Company, +1 9732906000, medical.information@themedco.com |
| Scientific contact           | Global Health Science Center, The Medicines Company, +1 9732906000, medical.information@themedco.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|                                                      |              |
|------------------------------------------------------|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 07 June 2017 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 07 June 2017 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the effect of inclisiran treatment on low-density lipoprotein cholesterol (LDL-C) levels at Day 180.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 01 December 2015 |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Efficacy, Safety |
| Long term follow-up duration                              | 5 Months         |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Canada: 71         |
| Country: Number of subjects enrolled | United States: 84  |
| Country: Number of subjects enrolled | Netherlands: 169   |
| Country: Number of subjects enrolled | United Kingdom: 86 |
| Country: Number of subjects enrolled | Germany: 91        |
| Worldwide total number of subjects   | 501                |
| EEA total number of subjects         | 346                |

Notes:

### Subjects enrolled per age group

|                                           |   |
|-------------------------------------------|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |
| Children (2-11 years)                     | 0 |

|                           |     |
|---------------------------|-----|
| Adolescents (12-17 years) | 0   |
| Adults (18-64 years)      | 253 |
| From 65 to 84 years       | 245 |
| 85 years and over         | 3   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

This study included male or female participants  $\geq 18$  years of age with a history of atherosclerotic cardiovascular disease (ASCVD) or ASCVD-risk equivalents or a  $>20\%$  ten-year risk of a cardiovascular (CV) event assessed by Framingham Risk Score or equivalent and receiving maximum-tolerated lipid-lowering therapy.

### 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                | Investigator, Subject          |

Blinding implementation details:

The study drug was blinded within each injection regimen: either 1 or 2 injections on Day 1 or a single injection on Day 1 and on Day 90. Study drug was prepared by the unblinded hospital pharmacist and was dispensed in a blinded syringe as randomized by the interactive web response system. Blinding was achieved by placing an over label on each unique syringe dispensed by the pharmacist, masking the color of the solution within because inclisiran could be visually distinguishable from placebo.

### Arms

|                              |             |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes         |
| <b>Arm title</b>             | Single Dose |

Arm description:

Participants received 1 of 3 different doses (200 milligrams [mg], 300 mg, or 500 mg) of inclisiran or matching placebo on Day 1. These 4 groups received no further study drug or placebo.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Inclisiran             |
| Investigational medicinal product code |                        |
| Other name                             | ALN-PCSSC              |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

All eligible participants were randomized and received their first subcutaneous (SC) injection of inclisiran (200 mg, 300 mg, or 500 mg) on Day 1. The 500-mg dose was administered as 2 injections, 1 of 300 mg (1.5 milliliters [mL]) and 1 of 200 mg (1.0 mL) in 2 different injection sites. A volume of 1.5 mL was the maximum injection volume for a single injection site.

|                                        |                                |
|----------------------------------------|--------------------------------|
| Investigational medicinal product name | Placebo                        |
| Investigational medicinal product code |                                |
| Other name                             | Saline (sterile, normal, 0.9%) |
| Pharmaceutical forms                   | Solution for injection         |
| Routes of administration               | Subcutaneous use               |

Dosage and administration details:

Placebo was administered as an SC injection in an amount matched to the doses within the Single Dose Arm.

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | Double Dose |
|------------------|-------------|

Arm description:

Participants received 1 of 3 different doses (100 mg, 200 mg, or 300 mg) of inclisiran or matching placebo on Day 1. These 4 groups then received a second dose on Day 90.

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

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Inclisiran             |
| Investigational medicinal product code |                        |
| Other name                             | ALN-PCSSC              |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

All eligible participants were randomized and received their SC injections of inclisiran (100 mg, 200 mg, or 300 mg) on Days 1 and 90. A volume of 1.5 mL was the maximum injection volume for a single injection.

|                                        |                                |
|----------------------------------------|--------------------------------|
| Investigational medicinal product name | Placebo                        |
| Investigational medicinal product code |                                |
| Other name                             | Saline (sterile, normal, 0.9%) |
| Pharmaceutical forms                   | Solution for injection         |
| Routes of administration               | Subcutaneous use               |

Dosage and administration details:

Placebo was administered as an SC injection in an amount matched to the doses within the Double Dose Arm.

| <b>Number of subjects in period 1</b> | Single Dose | Double Dose |
|---------------------------------------|-------------|-------------|
| Started                               | 253         | 248         |
| Completed                             | 236         | 233         |
| Not completed                         | 17          | 15          |
| Physician decision                    | 1           | 1           |
| Consent withdrawn by subject          | 6           | 7           |
| Adverse event, non-fatal              | 3           | 4           |
| Death                                 | 1           | 1           |
| Other                                 | 4           | 2           |
| Lost to follow-up                     | 2           | -           |

## Baseline characteristics

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Single Dose |
|-----------------------|-------------|

Reporting group description:

Participants received 1 of 3 different doses (200 milligrams [mg], 300 mg, or 500 mg) of inclisiran or matching placebo on Day 1. These 4 groups received no further study drug or placebo.

|                       |             |
|-----------------------|-------------|
| Reporting group title | Double Dose |
|-----------------------|-------------|

Reporting group description:

Participants received 1 of 3 different doses (100 mg, 200 mg, or 300 mg) of inclisiran or matching placebo on Day 1. These 4 groups then received a second dose on Day 90.

| Reporting group values                    | Single Dose | Double Dose | Total |
|-------------------------------------------|-------------|-------------|-------|
| Number of subjects                        | 253         | 248         | 501   |
| Age categorical                           |             |             |       |
| Units: Subjects                           |             |             |       |
| Adults (18-64 years)                      | 129         | 124         | 253   |
| From 65-84 years                          | 123         | 122         | 245   |
| 85 years and over                         | 1           | 2           | 3     |
| Age continuous                            |             |             |       |
| Units: years                              |             |             |       |
| arithmetic mean                           | 63          | 63.6        |       |
| standard deviation                        | ± 11.9      | ± 10        | -     |
| Gender categorical                        |             |             |       |
| Units: Subjects                           |             |             |       |
| Female                                    | 83          | 92          | 175   |
| Male                                      | 170         | 156         | 326   |
| Race                                      |             |             |       |
| Units: Subjects                           |             |             |       |
| American Indian or Alaska Native          | 3           | 3           | 6     |
| Asian                                     | 6           | 3           | 9     |
| Black or African                          | 10          | 8           | 18    |
| Native Hawaiian or Other Pacific Islander | 1           | 0           | 1     |
| White                                     | 231         | 234         | 465   |
| Undisclosed                               | 2           | 0           | 2     |
| Ethnicity                                 |             |             |       |
| Units: Subjects                           |             |             |       |
| Hispanic or Latino                        | 15          | 14          | 29    |
| Not Hispanic or Latino                    | 238         | 234         | 472   |

### Subject analysis sets

|                            |                                  |
|----------------------------|----------------------------------|
| Subject analysis set title | Intent-to-Treat (ITT) Population |
|----------------------------|----------------------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

All participants randomized into the trial. Treatment classification was based on the randomized treatment. This population was used to assess the randomness of treatment allocation.

|                            |                                            |
|----------------------------|--------------------------------------------|
| Subject analysis set title | Modified Intent-to-Treat (mITT) Population |
|----------------------------|--------------------------------------------|

|                           |                             |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

Subject analysis set description:

All randomized participants who received at least 1 dose of study drug and had both the baseline and the 180-day follow-up LDL-C assessment. Treatment classification was based on the randomized treatment. This was the primary population for analysis of the primary and secondary endpoints.

|                            |                     |
|----------------------------|---------------------|
| Subject analysis set title | Single Dose Placebo |
| Subject analysis set type  | Sub-group analysis  |

Subject analysis set description:

Participants received an SC injection of placebo (0.9% saline) in amounts matched to the doses administered in the Single Dose Arm.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Single Dose 200 mg |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants in this group received a 200-mg SC injection of inclisiran on Day 1 of the study.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Single Dose 300 mg |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants in this group received a 300-mg SC injection of inclisiran on Day 1 of the study.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Single Dose 500 mg |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

On Day 1 of the study, participants in this group received a 500-mg dose of inclisiran as 2 injections, 1 of 300 mg and 1 of 200 mg.

|                            |                     |
|----------------------------|---------------------|
| Subject analysis set title | Double Dose Placebo |
| Subject analysis set type  | Sub-group analysis  |

Subject analysis set description:

Participants received SC injections of placebo (0.9% saline) in amounts matched to the doses administered in the Double Dose Arm.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Double Dose 100 mg |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants in this group received their first 100-mg SC injection of inclisiran on Day 1 of the study. This was followed by a second injection on Day 90.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Double Dose 200 mg |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants in this group received their first 200-mg SC injection of inclisiran on Day 1 of the study. This was followed by a second injection on Day 90.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Double Dose 300 mg |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants in this group received their first 300-mg SC injection of inclisiran on Day 1 of the study. This was followed by a second injection on Day 90.

|                            |                                |
|----------------------------|--------------------------------|
| Subject analysis set title | Single and Double Dose Placebo |
| Subject analysis set type  | Sub-group analysis             |

Subject analysis set description:

This analysis includes all participants in both the single dose and the double dose placebo groups.

|                            |                               |
|----------------------------|-------------------------------|
| Subject analysis set title | Single and Double Dose 200 mg |
| Subject analysis set type  | Sub-group analysis            |

Subject analysis set description:

This analysis includes all participants in both the single dose and the double dose 200 mg groups.

|                            |                               |
|----------------------------|-------------------------------|
| Subject analysis set title | Single and Double Dose 300 mg |
| Subject analysis set type  | Sub-group analysis            |

Subject analysis set description:

This analysis includes all participants in both the single dose and the double dose 300 mg groups.

| Reporting group values                    | Intent-to-Treat (ITT)<br>Population | Modified Intent-to-Treat (mITT)<br>Population | Single Dose Placebo |
|-------------------------------------------|-------------------------------------|-----------------------------------------------|---------------------|
| Number of subjects                        | 501                                 | 483                                           | 65                  |
| Age categorical<br>Units: Subjects        |                                     |                                               |                     |
| Adults (18-64 years)                      | 253                                 | 243                                           | 40                  |
| From 65-84 years                          | 245                                 | 237                                           | 24                  |
| 85 years and over                         | 3                                   | 3                                             | 1                   |
| Age continuous<br>Units: years            |                                     |                                               |                     |
| arithmetic mean                           | 63.3                                | 63.4                                          | 62                  |
| standard deviation                        | ± 10.97                             | ± 11.01                                       | ± 11.4              |
| Gender categorical<br>Units: Subjects     |                                     |                                               |                     |
| Female                                    | 175                                 | 170                                           | 23                  |
| Male                                      | 326                                 | 313                                           | 42                  |
| Race<br>Units: Subjects                   |                                     |                                               |                     |
| American Indian or Alaska Native          | 6                                   | 5                                             | 1                   |
| Asian                                     | 9                                   | 8                                             | 0                   |
| Black or African                          | 18                                  | 16                                            | 4                   |
| Native Hawaiian or Other Pacific Islander | 1                                   | 1                                             | 0                   |
| White                                     | 465                                 | 451                                           | 59                  |
| Undisclosed                               | 2                                   | 2                                             | 1                   |
| Ethnicity<br>Units: Subjects              |                                     |                                               |                     |
| Hispanic or Latino                        | 29                                  | 29                                            | 7                   |
| Not Hispanic or Latino                    | 472                                 | 454                                           | 58                  |

| Reporting group values                | Single Dose 200 mg | Single Dose 300 mg | Single Dose 500 mg |
|---------------------------------------|--------------------|--------------------|--------------------|
| Number of subjects                    | 60                 | 62                 | 66                 |
| Age categorical<br>Units: Subjects    |                    |                    |                    |
| Adults (18-64 years)                  | 30                 | 27                 | 32                 |
| From 65-84 years                      | 30                 | 35                 | 34                 |
| 85 years and over                     | 0                  | 0                  | 0                  |
| Age continuous<br>Units: years        |                    |                    |                    |
| arithmetic mean                       | 63.9               | 64.1               | 62.1               |
| standard deviation                    | ± 10.8             | ± 12.8             | ± 12.4             |
| Gender categorical<br>Units: Subjects |                    |                    |                    |
| Female                                | 21                 | 20                 | 19                 |
| Male                                  | 39                 | 42                 | 47                 |
| Race<br>Units: Subjects               |                    |                    |                    |
| American Indian or Alaska Native      | 0                  | 1                  | 1                  |
| Asian                                 | 2                  | 2                  | 2                  |
| Black or African                      | 4                  | 2                  | 0                  |

|                                           |    |    |    |
|-------------------------------------------|----|----|----|
| Native Hawaiian or Other Pacific Islander | 0  | 1  | 0  |
| White                                     | 53 | 56 | 63 |
| Undisclosed                               | 1  | 0  | 0  |
| Ethnicity<br>Units: Subjects              |    |    |    |
| Hispanic or Latino                        | 4  | 3  | 1  |
| Not Hispanic or Latino                    | 56 | 59 | 65 |

| Reporting group values                    | Double Dose Placebo | Double Dose 100 mg | Double Dose 200 mg |
|-------------------------------------------|---------------------|--------------------|--------------------|
| Number of subjects                        | 62                  | 62                 | 63                 |
| Age categorical<br>Units: Subjects        |                     |                    |                    |
| Adults (18-64 years)                      | 32                  | 24                 | 37                 |
| From 65-84 years                          | 29                  | 38                 | 26                 |
| 85 years and over                         | 1                   | 0                  | 0                  |
| Age continuous<br>Units: years            |                     |                    |                    |
| arithmetic mean                           | 62.8                | 65.2               | 62.3               |
| standard deviation                        | ± 10.3              | ± 9.4              | ± 10.8             |
| Gender categorical<br>Units: Subjects     |                     |                    |                    |
| Female                                    | 29                  | 23                 | 24                 |
| Male                                      | 33                  | 39                 | 39                 |
| Race<br>Units: Subjects                   |                     |                    |                    |
| American Indian or Alaska Native          | 0                   | 2                  | 0                  |
| Asian                                     | 1                   | 1                  | 0                  |
| Black or African                          | 3                   | 2                  | 2                  |
| Native Hawaiian or Other Pacific Islander | 0                   | 0                  | 0                  |
| White                                     | 58                  | 57                 | 61                 |
| Undisclosed                               | 0                   |                    | 0                  |
| Ethnicity<br>Units: Subjects              |                     |                    |                    |
| Hispanic or Latino                        | 2                   | 2                  | 6                  |
| Not Hispanic or Latino                    | 60                  | 60                 | 57                 |

| Reporting group values             | Double Dose 300 mg | Single and Double Dose Placebo | Single and Double Dose 200 mg |
|------------------------------------|--------------------|--------------------------------|-------------------------------|
| Number of subjects                 | 61                 | 127                            | 123                           |
| Age categorical<br>Units: Subjects |                    |                                |                               |
| Adults (18-64 years)               | 31                 | 72                             | 67                            |
| From 65-84 years                   | 29                 | 53                             | 56                            |
| 85 years and over                  | 1                  | 2                              | 0                             |
| Age continuous<br>Units: years     |                    |                                |                               |
| arithmetic mean                    | 64.1               | 62.4                           | 63.1                          |
| standard deviation                 | ± 9.4              | ± 10.8                         | ± 10.8                        |

|                                           |    |     |     |
|-------------------------------------------|----|-----|-----|
| Gender categorical                        |    |     |     |
| Units: Subjects                           |    |     |     |
| Female                                    | 16 | 52  | 45  |
| Male                                      | 45 | 75  | 78  |
| Race                                      |    |     |     |
| Units: Subjects                           |    |     |     |
| American Indian or Alaska Native          | 1  | 1   | 0   |
| Asian                                     | 1  | 1   | 2   |
| Black or African                          | 1  | 7   | 6   |
| Native Hawaiian or Other Pacific Islander | 0  | 0   | 0   |
| White                                     | 58 | 117 | 114 |
| Undisclosed                               | 0  | 1   | 1   |
| Ethnicity                                 |    |     |     |
| Units: Subjects                           |    |     |     |
| Hispanic or Latino                        | 4  | 9   | 10  |
| Not Hispanic or Latino                    | 57 | 118 | 113 |

|                                           |                               |  |  |
|-------------------------------------------|-------------------------------|--|--|
| <b>Reporting group values</b>             | Single and Double Dose 300 mg |  |  |
| Number of subjects                        | 123                           |  |  |
| Age categorical                           |                               |  |  |
| Units: Subjects                           |                               |  |  |
| Adults (18-64 years)                      | 58                            |  |  |
| From 65-84 years                          | 64                            |  |  |
| 85 years and over                         | 1                             |  |  |
| Age continuous                            |                               |  |  |
| Units: years                              |                               |  |  |
| arithmetic mean                           | 64.1                          |  |  |
| standard deviation                        | ± 11.2                        |  |  |
| Gender categorical                        |                               |  |  |
| Units: Subjects                           |                               |  |  |
| Female                                    | 36                            |  |  |
| Male                                      | 87                            |  |  |
| Race                                      |                               |  |  |
| Units: Subjects                           |                               |  |  |
| American Indian or Alaska Native          | 2                             |  |  |
| Asian                                     | 3                             |  |  |
| Black or African                          | 3                             |  |  |
| Native Hawaiian or Other Pacific Islander | 1                             |  |  |
| White                                     | 114                           |  |  |
| Undisclosed                               | 0                             |  |  |
| Ethnicity                                 |                               |  |  |
| Units: Subjects                           |                               |  |  |
| Hispanic or Latino                        | 7                             |  |  |
| Not Hispanic or Latino                    | 116                           |  |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                        |                                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                  | Single Dose                                |
| Reporting group description:<br>Participants received 1 of 3 different doses (200 milligrams [mg], 300 mg, or 500 mg) of inclisiran or matching placebo on Day 1. These 4 groups received no further study drug or placebo.                                                                                                            |                                            |
| Reporting group title                                                                                                                                                                                                                                                                                                                  | Double Dose                                |
| Reporting group description:<br>Participants received 1 of 3 different doses (100 mg, 200 mg, or 300 mg) of inclisiran or matching placebo on Day 1. These 4 groups then received a second dose on Day 90.                                                                                                                             |                                            |
| Subject analysis set title                                                                                                                                                                                                                                                                                                             | Intent-to-Treat (ITT) Population           |
| Subject analysis set type                                                                                                                                                                                                                                                                                                              | Intention-to-treat                         |
| Subject analysis set description:<br>All participants randomized into the trial. Treatment classification was based on the randomized treatment. This population was used to assess the randomness of treatment allocation.                                                                                                            |                                            |
| Subject analysis set title                                                                                                                                                                                                                                                                                                             | Modified Intent-to-Treat (mITT) Population |
| Subject analysis set type                                                                                                                                                                                                                                                                                                              | Modified intention-to-treat                |
| Subject analysis set description:<br>All randomized participants who received at least 1 dose of study drug and had both the baseline and the 180-day follow-up LDL-C assessment. Treatment classification was based on the randomized treatment. This was the primary population for analysis of the primary and secondary endpoints. |                                            |
| Subject analysis set title                                                                                                                                                                                                                                                                                                             | Single Dose Placebo                        |
| Subject analysis set type                                                                                                                                                                                                                                                                                                              | Sub-group analysis                         |
| Subject analysis set description:<br>Participants received an SC injection of placebo (0.9% saline) in amounts matched to the doses administered in the Single Dose Arm.                                                                                                                                                               |                                            |
| Subject analysis set title                                                                                                                                                                                                                                                                                                             | Single Dose 200 mg                         |
| Subject analysis set type                                                                                                                                                                                                                                                                                                              | Sub-group analysis                         |
| Subject analysis set description:<br>Participants in this group received a 200-mg SC injection of inclisiran on Day 1 of the study.                                                                                                                                                                                                    |                                            |
| Subject analysis set title                                                                                                                                                                                                                                                                                                             | Single Dose 300 mg                         |
| Subject analysis set type                                                                                                                                                                                                                                                                                                              | Sub-group analysis                         |
| Subject analysis set description:<br>Participants in this group received a 300-mg SC injection of inclisiran on Day 1 of the study.                                                                                                                                                                                                    |                                            |
| Subject analysis set title                                                                                                                                                                                                                                                                                                             | Single Dose 500 mg                         |
| Subject analysis set type                                                                                                                                                                                                                                                                                                              | Sub-group analysis                         |
| Subject analysis set description:<br>On Day 1 of the study, participants in this group received a 500-mg dose of inclisiran as 2 injections, 1 of 300 mg and 1 of 200 mg.                                                                                                                                                              |                                            |
| Subject analysis set title                                                                                                                                                                                                                                                                                                             | Double Dose Placebo                        |
| Subject analysis set type                                                                                                                                                                                                                                                                                                              | Sub-group analysis                         |
| Subject analysis set description:<br>Participants received SC injections of placebo (0.9% saline) in amounts matched to the doses administered in the Double Dose Arm.                                                                                                                                                                 |                                            |
| Subject analysis set title                                                                                                                                                                                                                                                                                                             | Double Dose 100 mg                         |
| Subject analysis set type                                                                                                                                                                                                                                                                                                              | Sub-group analysis                         |
| Subject analysis set description:<br>Participants in this group received their first 100-mg SC injection of inclisiran on Day 1 of the study. This was followed by a second injection on Day 90.                                                                                                                                       |                                            |
| Subject analysis set title                                                                                                                                                                                                                                                                                                             | Double Dose 200 mg                         |
| Subject analysis set type                                                                                                                                                                                                                                                                                                              | Sub-group analysis                         |

Subject analysis set description:

Participants in this group received their first 200-mg SC injection of inclisiran on Day 1 of the study. This was followed by a second injection on Day 90.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Double Dose 300 mg |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants in this group received their first 300-mg SC injection of inclisiran on Day 1 of the study. This was followed by a second injection on Day 90.

|                            |                                |
|----------------------------|--------------------------------|
| Subject analysis set title | Single and Double Dose Placebo |
| Subject analysis set type  | Sub-group analysis             |

Subject analysis set description:

This analysis includes all participants in both the single dose and the double dose placebo groups.

|                            |                               |
|----------------------------|-------------------------------|
| Subject analysis set title | Single and Double Dose 200 mg |
| Subject analysis set type  | Sub-group analysis            |

Subject analysis set description:

This analysis includes all participants in both the single dose and the double dose 200 mg groups.

|                            |                               |
|----------------------------|-------------------------------|
| Subject analysis set title | Single and Double Dose 300 mg |
| Subject analysis set type  | Sub-group analysis            |

Subject analysis set description:

This analysis includes all participants in both the single dose and the double dose 300 mg groups.

### **Primary: Change From Baseline In LDL-C Levels For Single-Dose Inclisiran At Day 180**

|                 |                                                                            |
|-----------------|----------------------------------------------------------------------------|
| End point title | Change From Baseline In LDL-C Levels For Single-Dose Inclisiran At Day 180 |
|-----------------|----------------------------------------------------------------------------|

End point description:

This outcome measure evaluated the effect of single-dose (200 mg, 300 mg, 500 mg) inclisiran treatments on LDL-C levels in the mITT population at Day 180. The least square (LS) mean was calculated using a repeated measurement linear effect model. The model included treatment group, baseline value, scheduled visit, and the interaction of treatment group with scheduled visit. The p value was adjusted for multiple comparisons using Dunnett's Test.

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

End point timeframe:

Baseline, Day 180

| <b>End point values</b>                      | Single Dose Placebo  | Single Dose 200 mg     | Single Dose 300 mg     | Single Dose 500 mg     |
|----------------------------------------------|----------------------|------------------------|------------------------|------------------------|
| Subject group type                           | Subject analysis set | Subject analysis set   | Subject analysis set   | Subject analysis set   |
| Number of subjects analysed                  | 64                   | 60                     | 60                     | 60                     |
| Units: percent change                        |                      |                        |                        |                        |
| least squares mean (confidence interval 95%) | 2.1 (-2.9 to 7.2)    | -27.9 (-33.1 to -22.7) | -38.4 (-43.6 to -33.2) | -41.9 (-47.2 to -36.7) |

### **Statistical analyses**

|                                   |                       |
|-----------------------------------|-----------------------|
| <b>Statistical analysis title</b> | Placebo versus 200 mg |
|-----------------------------------|-----------------------|

Statistical analysis description:

Two-sample t-tests were performed to test the superiority of any dosing group over placebo.

|                   |                                          |
|-------------------|------------------------------------------|
| Comparison groups | Single Dose Placebo v Single Dose 200 mg |
|-------------------|------------------------------------------|

|                                         |                         |
|-----------------------------------------|-------------------------|
| Number of subjects included in analysis | 124                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | < 0.0001 <sup>[1]</sup> |
| Method                                  | Dunnett's Test          |
| Parameter estimate                      | Treatment Difference    |

Notes:

[1] - The p value was adjusted for multiple comparisons using Dunnett's Test.

|                                   |                       |
|-----------------------------------|-----------------------|
| <b>Statistical analysis title</b> | Placebo versus 300 mg |
|-----------------------------------|-----------------------|

Statistical analysis description:

Two-sample t-tests were performed to test the superiority of any dosing group over placebo.

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| Comparison groups                       | Single Dose Placebo v Single Dose 300 mg |
| Number of subjects included in analysis | 124                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | < 0.0001 <sup>[2]</sup>                  |
| Method                                  | Dunnett's Test                           |
| Parameter estimate                      | Treatment Difference                     |

Notes:

[2] - The p value was adjusted for multiple comparisons using Dunnett's Test.

|                                   |                       |
|-----------------------------------|-----------------------|
| <b>Statistical analysis title</b> | Placebo versus 500 mg |
|-----------------------------------|-----------------------|

Statistical analysis description:

Two-sample t-tests were performed to test the superiority of any dosing group over placebo.

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| Comparison groups                       | Single Dose Placebo v Single Dose 500 mg |
| Number of subjects included in analysis | 124                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | < 0.0001 <sup>[3]</sup>                  |
| Method                                  | Dunnett's Test                           |
| Parameter estimate                      | Treatment Difference                     |

Notes:

[3] - The p value was adjusted for multiple comparisons using Dunnett's Test.

## **Primary: Change From Baseline In LDL-C Levels For Double-Dose Inclisiran At Day 180**

|                 |                                                                            |
|-----------------|----------------------------------------------------------------------------|
| End point title | Change From Baseline In LDL-C Levels For Double-Dose Inclisiran At Day 180 |
|-----------------|----------------------------------------------------------------------------|

End point description:

This outcome measure evaluated the effect of double-dose (100 mg, 200 mg, 300 mg) inclisiran treatments on LDL-C levels in the mITT population at Day 180. The LS mean was calculated using a repeated measurement linear effect model. The model included treatment group, baseline value, scheduled visit, and the interaction of treatment group with scheduled visit. The p value was adjusted for multiple comparisons using Dunnett's Test.

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

End point timeframe:

Baseline, Day 180

| <b>End point values</b>                      | Double Dose Placebo  | Double Dose 100 mg   | Double Dose 200 mg     | Double Dose 300 mg     |
|----------------------------------------------|----------------------|----------------------|------------------------|------------------------|
| Subject group type                           | Subject analysis set | Subject analysis set | Subject analysis set   | Subject analysis set   |
| Number of subjects analysed                  | 61                   | 59                   | 60                     | 59                     |
| Units: percent change                        |                      |                      |                        |                        |
| least squares mean (confidence interval 95%) | 1.8 (-2.6 to 6.3)    | -35.5 (-40 to -31)   | -44.9 (-49.3 to -40.4) | -52.6 (-57.1 to -48.1) |

## Statistical analyses

| <b>Statistical analysis title</b>                                                                                                | Placebo versus 100 mg                    |
|----------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| Statistical analysis description:<br>Two-sample t-tests were performed to test the superiority of any dosing group over placebo. |                                          |
| Comparison groups                                                                                                                | Double Dose Placebo v Double Dose 100 mg |
| Number of subjects included in analysis                                                                                          | 120                                      |
| Analysis specification                                                                                                           | Pre-specified                            |
| Analysis type                                                                                                                    | superiority                              |
| P-value                                                                                                                          | < 0.0001 <sup>[4]</sup>                  |
| Method                                                                                                                           | Dunnett's Test                           |
| Parameter estimate                                                                                                               | Treatment Difference                     |

Notes:

[4] - The p value was adjusted for multiple comparisons using Dunnett's Test.

| <b>Statistical analysis title</b>                                                                                                | Placebo versus 200 mg                    |
|----------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| Statistical analysis description:<br>Two-sample t-tests were performed to test the superiority of any dosing group over placebo. |                                          |
| Comparison groups                                                                                                                | Double Dose Placebo v Double Dose 200 mg |
| Number of subjects included in analysis                                                                                          | 121                                      |
| Analysis specification                                                                                                           | Pre-specified                            |
| Analysis type                                                                                                                    | superiority <sup>[5]</sup>               |
| P-value                                                                                                                          | < 0.0001                                 |
| Method                                                                                                                           | Dunnett's Test                           |
| Parameter estimate                                                                                                               | Treatment Difference                     |

Notes:

[5] - The p value was adjusted for multiple comparisons using Dunnett's Test.

| <b>Statistical analysis title</b>                                                                                                | Placebo versus 300 mg                    |
|----------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| Statistical analysis description:<br>Two-sample t-tests were performed to test the superiority of any dosing group over placebo. |                                          |
| Comparison groups                                                                                                                | Double Dose Placebo v Double Dose 300 mg |

|                                         |                         |
|-----------------------------------------|-------------------------|
| Number of subjects included in analysis | 120                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | < 0.0001 <sup>[6]</sup> |
| Method                                  | Dunnett's Test          |
| Parameter estimate                      | Treatment Difference    |

Notes:

[6] - The p value was adjusted for multiple comparisons using Dunnett's Test.

### Secondary: Change From Baseline In LDL-C Levels at Day 90

|                                                                                                                                                                                                                                                                                                                                                   |                                                |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                   | Change From Baseline In LDL-C Levels at Day 90 |
| End point description:                                                                                                                                                                                                                                                                                                                            |                                                |
| This outcome measure evaluated the effects of single- and double-dose inclisiran on LDL-C levels in the mITT population at Day 90. The LS mean was calculated using a repeated measurement linear effect model. The model included treatment group, baseline value, scheduled visit, and the interaction of treatment group with scheduled visit. |                                                |
| End point type                                                                                                                                                                                                                                                                                                                                    | Secondary                                      |
| End point timeframe:                                                                                                                                                                                                                                                                                                                              |                                                |
| Baseline, Day 90                                                                                                                                                                                                                                                                                                                                  |                                                |

| End point values                             | Single Dose<br>500 mg | Double Dose<br>100 mg  | Single and<br>Double Dose<br>Placebo | Single and<br>Double Dose<br>200 mg |
|----------------------------------------------|-----------------------|------------------------|--------------------------------------|-------------------------------------|
| Subject group type                           | Subject analysis set  | Subject analysis set   | Subject analysis set                 | Subject analysis set                |
| Number of subjects analysed                  | 60                    | 59                     | 125                                  | 120                                 |
| Units: participants                          |                       |                        |                                      |                                     |
| least squares mean (confidence interval 95%) | -49 (-53.8 to -44.2)  | -34.2 (-39.1 to -29.3) | -0.8 (-4.2 to 2.5)                   | -41.8 (-45.3 to -38.4)              |

| End point values                             | Single and<br>Double Dose<br>300 mg |  |  |  |
|----------------------------------------------|-------------------------------------|--|--|--|
| Subject group type                           | Subject analysis set                |  |  |  |
| Number of subjects analysed                  | 118                                 |  |  |  |
| Units: participants                          |                                     |  |  |  |
| least squares mean (confidence interval 95%) | -45.7 (-49.2 to -42.3)              |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline In LDL-C Levels At Day 60, Day 120, and Day 210

|                 |                                                                      |
|-----------------|----------------------------------------------------------------------|
| End point title | Change From Baseline In LDL-C Levels At Day 60, Day 120, and Day 210 |
|-----------------|----------------------------------------------------------------------|

End point description:

This outcome measure evaluated the effects of both single- and double-dose inclisiran on LDL-C levels in the mITT population from baseline to Day 60, Day 120, and Day 210.

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

End point timeframe:

Baseline, Day 60, Day 120, and Day 210

| End point values                          | Single Dose Placebo   | Single Dose 200 mg        | Single Dose 300 mg        | Single Dose 500 mg        |
|-------------------------------------------|-----------------------|---------------------------|---------------------------|---------------------------|
| Subject group type                        | Subject analysis set  | Subject analysis set      | Subject analysis set      | Subject analysis set      |
| Number of subjects analysed               | 64 <sup>[7]</sup>     | 60 <sup>[8]</sup>         | 60                        | 60 <sup>[9]</sup>         |
| Units: percentage change                  |                       |                           |                           |                           |
| arithmetic mean (confidence interval 95%) |                       |                           |                           |                           |
| Day 60                                    | -4.27 (-7.84 to -0.7) | -44.32 (-50.55 to -38.09) | -50.87 (-55.62 to -46.12) | -49.58 (-54.12 to -45.04) |
| Day 120                                   | -0.91 (-5.17 to 3.34) | -36.94 (-42.8 to -31.08)  | -43.32 (-48.95 to -37.68) | -46.42 (-50.63 to -42.22) |
| Day 210                                   | 1.45 (-3.61 to 6.06)  | -28.98 (-36.83 to -21.12) | -35.39 (-41.47 to -29.31) | -39.2 (-43.71 to -34.68)  |

Notes:

[7] - Day 60 (62); Day 210 (62)

[8] - Day 120 (58)

[9] - Day 60 (58); Day 120 (57)

| End point values                          | Double Dose Placebo  | Double Dose 100 mg        | Double Dose 200 mg        | Double Dose 300 mg        |
|-------------------------------------------|----------------------|---------------------------|---------------------------|---------------------------|
| Subject group type                        | Subject analysis set | Subject analysis set      | Subject analysis set      | Subject analysis set      |
| Number of subjects analysed               | 61 <sup>[10]</sup>   | 59 <sup>[11]</sup>        | 60 <sup>[12]</sup>        | 59 <sup>[13]</sup>        |
| Units: percentage change                  |                      |                           |                           |                           |
| arithmetic mean (confidence interval 95%) |                      |                           |                           |                           |
| Day 60                                    | -1.92 (-6.7 to 2.85) | -35.73 (-40.23 to -31.23) | -44.28 (-49.1 to -39.47)  | -50.59 (-55.51 to -45.67) |
| Day 120                                   | 0.17 (-3.61 to 3.95) | -41.37 (-45.94 to -36.8)  | -49.54 (-54.6 to -44.49)  | -54.73 (-59.88 to -49.58) |
| Day 210                                   | 0.58 (-4.58 to 5.74) | -31.67 (-36.08 to -27.27) | -42.59 (-47.11 to -38.08) | -50.54 (-54.83 to -46.25) |

Notes:

[10] - Day 210 (60)

[11] - Day 90 (58); Day 120 (58)

[12] - Day 120 (59)

[13] - Day 120 (58); Day 210 (58)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion Of Participants With An LDL-C Greater Than 80% Of The Baseline Value At Day 180 and Day 210

|                 |                                                                                                        |
|-----------------|--------------------------------------------------------------------------------------------------------|
| End point title | Proportion Of Participants With An LDL-C Greater Than 80% Of The Baseline Value At Day 180 and Day 210 |
|-----------------|--------------------------------------------------------------------------------------------------------|

End point description:

This outcome measure evaluated the number of participants (single and double dose) in the mITT population with an LDL-C greater than 80% of the baseline value at Day 180 and Day 210.

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

End point timeframe:

Baseline, Day 180, Day 210

| End point values            | Single Dose<br>Placebo | Single Dose<br>200 mg | Single Dose<br>300 mg | Single Dose<br>500 mg |
|-----------------------------|------------------------|-----------------------|-----------------------|-----------------------|
| Subject group type          | Subject analysis set   | Subject analysis set  | Subject analysis set  | Subject analysis set  |
| Number of subjects analysed | 64 <sup>[14]</sup>     | 60                    | 60                    | 60                    |
| Units: participants         |                        |                       |                       |                       |
| Day 180                     | 35                     | 6                     | 5                     | 0                     |
| Day 210                     | 34                     | 8                     | 5                     | 2                     |

Notes:

[14] - Day 180 (64); Day 210 (62)

| End point values            | Double Dose<br>Placebo | Double Dose<br>100 mg | Double Dose<br>200 mg | Double Dose<br>300 mg |
|-----------------------------|------------------------|-----------------------|-----------------------|-----------------------|
| Subject group type          | Subject analysis set   | Subject analysis set  | Subject analysis set  | Subject analysis set  |
| Number of subjects analysed | 61 <sup>[15]</sup>     | 59                    | 60                    | 59                    |
| Units: participants         |                        |                       |                       |                       |
| Day 180                     | 29                     | 2                     | 1                     | 0                     |
| Day 210                     | 34                     | 1                     | 1                     | 1                     |

Notes:

[15] - Day 180 (61); Day 210 (60)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion Of Participants With Individual Responsiveness as Measured By LDL-C Levels At Day 90 and Day 180

|                 |                                                                                                             |
|-----------------|-------------------------------------------------------------------------------------------------------------|
| End point title | Proportion Of Participants With Individual Responsiveness as Measured By LDL-C Levels At Day 90 and Day 180 |
|-----------------|-------------------------------------------------------------------------------------------------------------|

End point description:

This outcome measure evaluated the individual responsiveness of participants to inclisiran (single and double dose) in the mITT population as defined by an LDL-C level of <25 mg/deciliter [dL] at Day 90 and Day 180.

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

End point timeframe:

Day 90, Day 180

| End point values            | Single Dose Placebo  | Single Dose 200 mg   | Single Dose 300 mg   | Single Dose 500 mg   |
|-----------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type          | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 64 <sup>[16]</sup>   | 60                   | 60 <sup>[17]</sup>   | 60                   |
| Units: participants         |                      |                      |                      |                      |
| Day 90                      | 0                    | 0                    | 5                    | 3                    |
| Day 180                     | 0                    | 0                    | 1                    | 2                    |

Notes:

[16] - Day 90 (63)

[17] - Day 90 (59)

| End point values            | Double Dose Placebo  | Double Dose 100 mg   | Double Dose 200 mg   | Double Dose 300 mg   |
|-----------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type          | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 61 <sup>[18]</sup>   | 59                   | 60                   | 59                   |
| Units: participants         |                      |                      |                      |                      |
| Day 90                      | 0                    | 0                    | 1                    | 0                    |
| Day 180                     | 0                    | 1                    | 2                    | 3                    |

Notes:

[18] - Day 90 (60)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion Of Participants With Greater Or Equal To 50% LDL-C Reduction From Baseline At Day 180

|                 |                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------|
| End point title | Proportion Of Participants With Greater Or Equal To 50% LDL-C Reduction From Baseline At Day 180 |
|-----------------|--------------------------------------------------------------------------------------------------|

End point description:

This outcome measure evaluated the number of participants (single and double dose) in the mITT population with an LDL-C reduction greater than 50% of the baseline value at Day 180.

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

End point timeframe:

Baseline, Day 180

| End point values            | Single Dose Placebo  | Single Dose 200 mg   | Single Dose 300 mg   | Single Dose 500 mg   |
|-----------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type          | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 64                   | 60                   | 60                   | 60                   |
| Units: participant          | 0                    | 9                    | 19                   | 16                   |

| End point values            | Double Dose Placebo  | Double Dose 100 mg   | Double Dose 200 mg   | Double Dose 300 mg   |
|-----------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type          | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 61                   | 59                   | 60                   | 59                   |
| Units: participant          | 0                    | 14                   | 27                   | 32                   |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage Change In PCSK9 Levels From Baseline At Day 180

|                 |                                                            |
|-----------------|------------------------------------------------------------|
| End point title | Percentage Change In PCSK9 Levels From Baseline At Day 180 |
|-----------------|------------------------------------------------------------|

End point description:

This outcome measure evaluated the percent change in proprotein convertase subtilisin/kexin type 9 (PCSK9) from baseline to Day 180 in participants (single and double dose) in the mITT population.

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

End point timeframe:

Baseline, Day 180

| End point values                     | Single Dose Placebo  | Single Dose 200 mg   | Single Dose 300 mg   | Single Dose 500 mg   |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                   | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed          | 64                   | 60                   | 60                   | 60                   |
| Units: percent change                |                      |                      |                      |                      |
| arithmetic mean (standard deviation) | 2.2 (± 23.4)         | -47.9 (± 21)         | -56 (± 19.2)         | -59.3 (± 18)         |

| End point values                     | Double Dose Placebo  | Double Dose 100 mg   | Double Dose 200 mg   | Double Dose 300 mg   |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                   | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed          | 61                   | 59                   | 60                   | 59                   |
| Units: percent change                |                      |                      |                      |                      |
| arithmetic mean (standard deviation) | -1.2 (± 20.7)        | -53.2 (± 20.9)       | -66.2 (± 15.6)       | -69.1 (± 12.1)       |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage Change In Other Lipids and Apolipoproteins From Baseline To Day 180

|                 |                                                                                |
|-----------------|--------------------------------------------------------------------------------|
| End point title | Percentage Change In Other Lipids and Apolipoproteins From Baseline To Day 180 |
|-----------------|--------------------------------------------------------------------------------|

End point description:

This outcome measure evaluated the percent change from baseline to Day 180 in cholesterol (total, high-density lipoprotein [HDL], non-HDL) and apolipoproteins (B, A1) in participants (single and double dose) in the mITT population.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Day 180    |           |

| End point values                     | Single Dose Placebo  | Single Dose 200 mg   | Single Dose 300 mg   | Single Dose 500 mg   |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                   | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed          | 64                   | 60                   | 60                   | 60                   |
| Units: percent change                |                      |                      |                      |                      |
| arithmetic mean (standard deviation) |                      |                      |                      |                      |
| Total Cholesterol                    | 1.8 (± 12.1)         | -17.6 (± 19)         | -23.7 (± 15.7)       | -26.6 (± 10.7)       |
| Non-HDL Cholesterol                  | 1.5 (± 16.7)         | -25.1 (± 26.2)       | -35.2 (± 20.2)       | -36.9 (± 14)         |
| HDL Cholesterol                      | 3.8 (± 15.6)         | 4.4 (± 14.8)         | 8.8 (± 11.1)         | 6.9 (± 14)           |
| Apolipoprotein B                     | 1.7 (± 14.7)         | -22.9 (± 21)         | -30.8 (± 18)         | -33.1 (± 12.7)       |
| Apolipoprotein A1                    | 3.6 (± 10.6)         | 2.9 (± 9.3)          | 3.8 (± 8.9)          | 4.1 (± 10.9)         |

| End point values                     | Double Dose Placebo  | Double Dose 100 mg   | Double Dose 200 mg   | Double Dose 300 mg   |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                   | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed          | 61                   | 59                   | 60                   | 59                   |
| Units: percent change                |                      |                      |                      |                      |
| arithmetic mean (standard deviation) |                      |                      |                      |                      |
| Total Cholesterol                    | 0.7 (± 12.3)         | -22.4 (± 12.4)       | -26.8 (± 13)         | -33.2 (± 11.3)       |
| Non-HDL Cholesterol                  | 1.3 (± 16.9)         | -31.7 (± 15.1)       | -38.9 (± 16.8)       | -46 (± 14.6)         |
| HDL Cholesterol                      | 0.5 (± 12.5)         | 7.6 (± 12.2)         | 10.3 (± 15.3)        | 8.6 (± 14.9)         |
| Apolipoprotein B                     | 0.9 (± 13)           | -27.8 (± 13.4)       | -35 (± 15.8)         | -40.9 (± 14.8)       |
| Apolipoprotein A1                    | 0.8 (± 8.3)          | 5.5 (± 10.6)         | 8.6 (± 11.5)         | 6.2 (± 11.9)         |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion Of Participants Who Attained Global Lipid Modification Targets For Level Of Atherosclerotic Cardiovascular Disease Risk

|                 |                                                                                                                                    |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Proportion Of Participants Who Attained Global Lipid Modification Targets For Level Of Atherosclerotic Cardiovascular Disease Risk |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------|

End point description:

This outcome measure evaluated the proportion of participants (single and double dose) in the mITT population who attained a global lipid modification target by baseline cardiovascular risk group, looking specifically at LDL-C levels (mg/dL) in the category of cardiovascular disease (CVD).

CVD was defined as a participant who had at least 1 of the following: prior myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass graft, prior stroke, prior transient ischemic attack, peripheral artery disease.

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

End point timeframe:

Baseline, Day 180

| End point values            | Single Dose<br>Placebo | Single Dose<br>200 mg | Single Dose<br>300 mg | Single Dose<br>500 mg |
|-----------------------------|------------------------|-----------------------|-----------------------|-----------------------|
| Subject group type          | Subject analysis set   | Subject analysis set  | Subject analysis set  | Subject analysis set  |
| Number of subjects analysed | 64                     | 60                    | 60                    | 60                    |
| Units: participant          |                        |                       |                       |                       |
| CVD                         | 45                     | 43                    | 46                    | 33                    |
| <70 mg/dL                   | 0                      | 16                    | 27                    | 18                    |

| End point values            | Double Dose<br>Placebo | Double Dose<br>100 mg | Double Dose<br>200 mg | Double Dose<br>300 mg |
|-----------------------------|------------------------|-----------------------|-----------------------|-----------------------|
| Subject group type          | Subject analysis set   | Subject analysis set  | Subject analysis set  | Subject analysis set  |
| Number of subjects analysed | 61                     | 59                    | 60                    | 59                    |
| Units: participant          |                        |                       |                       |                       |
| CVD                         | 45                     | 41                    | 39                    | 42                    |
| <70 mg/dL                   | 1                      | 24                    | 27                    | 33                    |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage Change In Other Lipids And Inflammatory Markers From Baseline To Day 180

|                 |                                                                                     |
|-----------------|-------------------------------------------------------------------------------------|
| End point title | Percentage Change In Other Lipids And Inflammatory Markers From Baseline To Day 180 |
|-----------------|-------------------------------------------------------------------------------------|

End point description:

This outcome measure evaluated the percent change from baseline to Day 180 in triglycerides, very-low-density lipoprotein (VLDL) cholesterol, lipoprotein(a), and high sensitivity C-reactive protein (hsCRP) in participants (single and double dose) in the mITT population.

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

End point timeframe:

Baseline, Day 180

| End point values                      | Single Dose<br>Placebo | Single Dose<br>200 mg | Single Dose<br>300 mg | Single Dose<br>500 mg |
|---------------------------------------|------------------------|-----------------------|-----------------------|-----------------------|
| Subject group type                    | Subject analysis set   | Subject analysis set  | Subject analysis set  | Subject analysis set  |
| Number of subjects analysed           | 64                     | 60                    | 60                    | 60                    |
| Units: percent change                 |                        |                       |                       |                       |
| median (inter-quartile range (Q1-Q3)) |                        |                       |                       |                       |
| Triglycerides                         | 6.4 (-15.9 to 21.9)    | 1.1 (-18.5 to 17.8)   | -12.8 (-27.8 to 7.8)  | -12.2 (-25.6 to 7.7)  |

|                  |                      |                       |                       |                      |
|------------------|----------------------|-----------------------|-----------------------|----------------------|
| VLDL Cholesterol | 2.4 (-30.7 to 30.5)  | -11.6 (-35.8 to 23.3) | -23.8 (-43 to -6.4)   | -14.6 (-34.8 to 3.5) |
| Lipoprotein(a)   | 0.5 (-13.9 to 14.8)  | -14.3 (-29.5 to -3.5) | -14.3 (-25.4 to -5.6) | -18.2 (-35 to -1.6)  |
| hsCRP            | -5.3 (-40.8 to 28.4) | 7.1 (-30.7 to 70.9)   | -16.2 (-45.8 to 50)   | -19.8 (-50 to 32.7)  |

| End point values                      | Double Dose Placebo  | Double Dose 100 mg    | Double Dose 200 mg    | Double Dose 300 mg     |
|---------------------------------------|----------------------|-----------------------|-----------------------|------------------------|
| Subject group type                    | Subject analysis set | Subject analysis set  | Subject analysis set  | Subject analysis set   |
| Number of subjects analysed           | 61                   | 59                    | 60                    | 59                     |
| Units: percent change                 |                      |                       |                       |                        |
| median (inter-quartile range (Q1-Q3)) |                      |                       |                       |                        |
| Triglycerides                         | -3 (-17.2 to 22.6)   | -6.3 (-17.6 to 10.9)  | 0.7 (-22.4 to 11.3)   | -14.2 (-26.4 to 5.4)   |
| VLDL Cholesterol                      | 2.7 (-20 to 26.7)    | -16.4 (-31.3 to 0)    | -21.2 (-38.5 to 13.2) | -16 (-38.2 to 9.1)     |
| Lipoprotein(a)                        | 0 (-10 to 12.4)      | -14.9 (-26.2 to -1.9) | -17.3 (-31.9 to -7.7) | -25.6 (-38.5 to -15.2) |
| hsCRP                                 | -20 (-50 to 30)      | -12.5 (-42.9 to 29.4) | -16.3 (-34.6 to 24.3) | -16.7 (-50.9 to 33.3)  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 360 days ( $\pm$  3 days) post randomization and treatment.

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

### Dictionary used

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

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

### Reporting groups

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Placebo - Single Dose |
|-----------------------|-----------------------|

Reporting group description:

Participants received an SC injection of placebo (0.9% saline) that matched the doses administered in the Single Dose Arm.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | 200 mg - Single Dose |
|-----------------------|----------------------|

Reporting group description:

Participants in this group only received a 200-mg SC injection of inclisiran on Day 1 of the study.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | 300 mg - Single Dose |
|-----------------------|----------------------|

Reporting group description:

Participants in this group only received a 300-mg SC injection of inclisiran on Day 1 of the study.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | 500 mg - Single Dose |
|-----------------------|----------------------|

Reporting group description:

On Day 1 only of the study, participants in this group received a 500-mg dose of inclisiran as 2 injections, 1 of 300 mg and 1 of 200 mg.

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Placebo - Double Dose |
|-----------------------|-----------------------|

Reporting group description:

Participants received SC injections of placebo (0.9% saline) in amounts that matched doses administered in the Double Dose Arm.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | 100 mg - Double Dose |
|-----------------------|----------------------|

Reporting group description:

Participants in this group received their first 100-mg SC injection of inclisiran on Day 1 of the study. This was followed by a second injection on Day 90.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | 200 mg - Double Dose |
|-----------------------|----------------------|

Reporting group description:

Participants in this group received their first 200-mg SC injection of inclisiran on Day 1 of the study. This was followed by a second injection on Day 90.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | 300 mg - Double Dose |
|-----------------------|----------------------|

Reporting group description:

Participants in this group received their first 300-mg SC injection of inclisiran on Day 1 of the study. This was followed by a second injection on Day 90.

| Serious adverse events                            | Placebo - Single Dose | 200 mg - Single Dose | 300 mg - Single Dose |
|---------------------------------------------------|-----------------------|----------------------|----------------------|
| Total subjects affected by serious adverse events |                       |                      |                      |
| subjects affected / exposed                       | 3 / 65 (4.62%)        | 11 / 60 (18.33%)     | 11 / 61 (18.03%)     |
| number of deaths (all causes)                     | 0                     | 0                    | 0                    |
| number of deaths resulting from adverse events    |                       |                      |                      |

|                                                                     |                |                |                |
|---------------------------------------------------------------------|----------------|----------------|----------------|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                |                |                |
| Hepatocellular carcinoma                                            |                |                |                |
| subjects affected / exposed                                         | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Prostate cancer                                                     |                |                |                |
| subjects affected / exposed                                         | 0 / 65 (0.00%) | 2 / 60 (3.33%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Squamous cell carcinoma of lung                                     |                |                |                |
| subjects affected / exposed                                         | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Tongue neoplasm malignant stage                                     |                |                |                |
| subjects affected / exposed                                         | 0 / 65 (0.00%) | 1 / 60 (1.67%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Adenocarcinoma of colon                                             |                |                |                |
| subjects affected / exposed                                         | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Bladder cancer                                                      |                |                |                |
| subjects affected / exposed                                         | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Glioblastoma                                                        |                |                |                |
| subjects affected / exposed                                         | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Intestinal adenocarcinoma                                           |                |                |                |
| subjects affected / exposed                                         | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Bladder transitional cell carcinoma stage 0     |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal tract adenoma                  |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Non-small cell lung cancer stage I              |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Oesophageal adenocarcinoma                      |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 1 / 60 (1.67%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pituitary tumour benign                         |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Squamous cell carcinoma of skin                 |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 1 / 60 (1.67%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Vascular disorders                              |                |                |                |
| Aortic dissection                               |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypotension                                     |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|                                                      |                |                |                |
|------------------------------------------------------|----------------|----------------|----------------|
| Orthostatic hypotension                              |                |                |                |
| subjects affected / exposed                          | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Intermittent claudication                            |                |                |                |
| subjects affected / exposed                          | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| Device dislocation                                   |                |                |                |
| subjects affected / exposed                          | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Pain                                                 |                |                |                |
| subjects affected / exposed                          | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Non-cardiac chest pain                               |                |                |                |
| subjects affected / exposed                          | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Stent-graft endoleak                                 |                |                |                |
| subjects affected / exposed                          | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Vascular stent restenosis                            |                |                |                |
| subjects affected / exposed                          | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders      |                |                |                |
| Chronic obstructive pulmonary disease                |                |                |                |

|                                                       |                |                |                |
|-------------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                           | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Investigations</b>                                 |                |                |                |
| Transaminases increased                               |                |                |                |
| subjects affected / exposed                           | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Haemoglobin decreased                                 |                |                |                |
| subjects affected / exposed                           | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Platelet count decreased                              |                |                |                |
| subjects affected / exposed                           | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Injury, poisoning and procedural complications</b> |                |                |                |
| Concussion                                            |                |                |                |
| subjects affected / exposed                           | 1 / 65 (1.54%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Thoracic vertebral fracture                           |                |                |                |
| subjects affected / exposed                           | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Traumatic haemothorax                                 |                |                |                |
| subjects affected / exposed                           | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Upper limb fracture                                   |                |                |                |
| subjects affected / exposed                           | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Facial bones fracture                           |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Humerus fracture                                |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Intentional overdose                            |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ligament sprain                                 |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Post procedural complication                    |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Post procedural haemorrhage                     |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Weaning failure                                 |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Limb crushing injury                            |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 1 / 60 (1.67%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Multiple injuries                               |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumothorax traumatic                          |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |                |                |                |
| Angina pectoris                                 |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 1 / 60 (1.67%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Angina unstable                                 |                |                |                |
| subjects affected / exposed                     | 1 / 65 (1.54%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Myocardial infarction                           |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 1 / 60 (1.67%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Acute myocardial infarction                     |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Atrial flutter                                  |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Atrial tachycardia                              |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Atrioventricular block complete                 |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Coronary artery disease                         |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Atrial fibrillation                             |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac arrest                                  |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pericarditis                                    |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ventricular extrasystoles                       |                |                |                |
| subjects affected / exposed                     | 1 / 65 (1.54%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Carpal tunnel syndrome                          |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 1 / 60 (1.67%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ischaemic stroke                                |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Lacunar stroke                                  |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Neuropathy peripheral                           |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Spinal cord ischaemia                           |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Syncope                                         |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 1 / 60 (1.67%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| Anaemia                                         |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Constipation                                    |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Inguinal hernia                                 |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 1 / 60 (1.67%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Proctitis ulcerative                            |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Aorto-oesophageal fistula                       |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastritis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Rectal haemorrhage                              |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Large intestine polyp                           |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Volvulus                                        |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 1 / 60 (1.67%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Vomiting                                        |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatobiliary disorders                         |                |                |                |
| Hepatic haemorrhage                             |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| Calculus urinary                                |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 1 / 60 (1.67%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Acute kidney injury                             |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Stress urinary incontinence                     |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Muscle necrosis                                 |                |                |                |
| subjects affected / exposed                     | 1 / 65 (1.54%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Osteitis                                        |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 1 / 60 (1.67%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Osteoarthritis                                  |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Urinary tract infection                         |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Appendicitis                                    |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Device related infection                        |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Erysipelas                                      |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastroenteritis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Implant site infection                          |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Listeria sepsis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Osteomyelitis                                   |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urosepsis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Wound abscess                                   |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |                |                |                |
| Dehydration                                     |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypoglycaemia                                   |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>                                       | 500 mg - Single Dose | Placebo - Double Dose | 100 mg - Double Dose |
|---------------------------------------------------------------------|----------------------|-----------------------|----------------------|
| Total subjects affected by serious adverse events                   |                      |                       |                      |
| subjects affected / exposed                                         | 8 / 65 (12.31%)      | 7 / 62 (11.29%)       | 13 / 61 (21.31%)     |
| number of deaths (all causes)                                       | 1                    | 0                     | 0                    |
| number of deaths resulting from adverse events                      |                      |                       |                      |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                      |                       |                      |
| Hepatocellular carcinoma                                            |                      |                       |                      |
| subjects affected / exposed                                         | 0 / 65 (0.00%)       | 0 / 62 (0.00%)        | 0 / 61 (0.00%)       |
| occurrences causally related to treatment / all                     | 0 / 0                | 0 / 0                 | 0 / 0                |
| deaths causally related to treatment / all                          | 0 / 0                | 0 / 0                 | 0 / 0                |
| Prostate cancer                                                     |                      |                       |                      |
| subjects affected / exposed                                         | 0 / 65 (0.00%)       | 0 / 62 (0.00%)        | 0 / 61 (0.00%)       |
| occurrences causally related to treatment / all                     | 0 / 0                | 0 / 0                 | 0 / 0                |
| deaths causally related to treatment / all                          | 0 / 0                | 0 / 0                 | 0 / 0                |
| Squamous cell carcinoma of lung                                     |                      |                       |                      |
| subjects affected / exposed                                         | 1 / 65 (1.54%)       | 0 / 62 (0.00%)        | 0 / 61 (0.00%)       |
| occurrences causally related to treatment / all                     | 0 / 1                | 0 / 0                 | 0 / 0                |
| deaths causally related to treatment / all                          | 0 / 0                | 0 / 0                 | 0 / 0                |
| Tongue neoplasm malignant stage                                     |                      |                       |                      |
| subjects affected / exposed                                         | 0 / 65 (0.00%)       | 0 / 62 (0.00%)        | 0 / 61 (0.00%)       |
| occurrences causally related to treatment / all                     | 0 / 0                | 0 / 0                 | 0 / 0                |
| deaths causally related to treatment / all                          | 0 / 0                | 0 / 0                 | 0 / 0                |
| Adenocarcinoma of colon                                             |                      |                       |                      |
| subjects affected / exposed                                         | 0 / 65 (0.00%)       | 0 / 62 (0.00%)        | 0 / 61 (0.00%)       |
| occurrences causally related to treatment / all                     | 0 / 0                | 0 / 0                 | 0 / 0                |
| deaths causally related to treatment / all                          | 0 / 0                | 0 / 0                 | 0 / 0                |
| Bladder cancer                                                      |                      |                       |                      |
| subjects affected / exposed                                         | 0 / 65 (0.00%)       | 0 / 62 (0.00%)        | 0 / 61 (0.00%)       |
| occurrences causally related to treatment / all                     | 0 / 0                | 0 / 0                 | 0 / 0                |
| deaths causally related to treatment / all                          | 0 / 0                | 0 / 0                 | 0 / 0                |

|                                             |                                                 |                |                |                |
|---------------------------------------------|-------------------------------------------------|----------------|----------------|----------------|
| Glioblastoma                                | subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
|                                             | occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
|                                             | deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Intestinal adenocarcinoma                   | subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
|                                             | occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
|                                             | deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bladder transitional cell carcinoma stage 0 | subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
|                                             | occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
|                                             | deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal tract adenoma              | subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
|                                             | occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
|                                             | deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Non-small cell lung cancer stage I          | subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
|                                             | occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
|                                             | deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Oesophageal adenocarcinoma                  | subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
|                                             | occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
|                                             | deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pituitary tumour benign                     | subjects affected / exposed                     | 1 / 65 (1.54%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
|                                             | occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
|                                             | deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Squamous cell carcinoma of skin             | subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
|                                             | occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
|                                             | deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Vascular disorders                          |                                                 |                |                |                |

|                                                      |                |                |                |
|------------------------------------------------------|----------------|----------------|----------------|
| Aortic dissection                                    |                |                |                |
| subjects affected / exposed                          | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypotension                                          |                |                |                |
| subjects affected / exposed                          | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Orthostatic hypotension                              |                |                |                |
| subjects affected / exposed                          | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Intermittent claudication                            |                |                |                |
| subjects affected / exposed                          | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| Device dislocation                                   |                |                |                |
| subjects affected / exposed                          | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Pain                                                 |                |                |                |
| subjects affected / exposed                          | 1 / 65 (1.54%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Non-cardiac chest pain                               |                |                |                |
| subjects affected / exposed                          | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Stent-graft endoleak                                 |                |                |                |
| subjects affected / exposed                          | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Vascular stent restenosis                       |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2          |
| 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 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Investigations                                  |                |                |                |
| Transaminases increased                         |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Haemoglobin decreased                           |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 1 / 62 (1.61%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Platelet count decreased                        |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 1 / 62 (1.61%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications  |                |                |                |
| Concussion                                      |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Thoracic vertebral fracture                     |                |                |                |
| subjects affected / exposed                     | 1 / 65 (1.54%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Traumatic haemothorax                           |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 65 (1.54%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Upper limb fracture                             |                |                |                |
| subjects affected / exposed                     | 1 / 65 (1.54%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Facial bones fracture                           |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Humerus fracture                                |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Intentional overdose                            |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 1 / 62 (1.61%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ligament sprain                                 |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Post procedural complication                    |                |                |                |
| subjects affected / exposed                     | 1 / 65 (1.54%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Post procedural haemorrhage                     |                |                |                |
| subjects affected / exposed                     | 1 / 65 (1.54%) | 1 / 62 (1.61%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Weaning failure                                 |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Limb crushing injury                            |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Multiple injuries                               |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumothorax traumatic                          |                |                |                |
| subjects affected / exposed                     | 1 / 65 (1.54%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |                |                |                |
| Angina pectoris                                 |                |                |                |
| subjects affected / exposed                     | 1 / 65 (1.54%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Angina unstable                                 |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Myocardial infarction                           |                |                |                |
| subjects affected / exposed                     | 2 / 65 (3.08%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| Acute myocardial infarction                     |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Atrial flutter                                  |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 65 (1.54%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Atrial tachycardia                              |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Atrioventricular block complete                 |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 1 / 62 (1.61%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Coronary artery disease                         |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Atrial fibrillation                             |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac arrest                                  |                |                |                |
| subjects affected / exposed                     | 1 / 65 (1.54%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pericarditis                                    |                |                |                |
| subjects affected / exposed                     | 1 / 65 (1.54%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ventricular extrasystoles                       |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Carpal tunnel syndrome                          |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ischaemic stroke                                |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Lacunar stroke                                  |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Neuropathy peripheral                           |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Spinal cord ischaemia                           |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Syncope                                         |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 1 / 62 (1.61%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| Anaemia                                         |                |                |                |
| subjects affected / exposed                     | 1 / 65 (1.54%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Constipation                                    |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Inguinal hernia                                 |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Proctitis ulcerative                            |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Aorto-oesophageal fistula                       |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastritis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Rectal haemorrhage                              |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 1 / 62 (1.61%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Large intestine polyp                           |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Volvulus                                        |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Vomiting                                        |                |                |                |
| subjects affected / exposed                     | 1 / 65 (1.54%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatobiliary disorders                         |                |                |                |
| Hepatic haemorrhage                             |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| Calculus urinary                                |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Acute kidney injury                             |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Stress urinary incontinence                     |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 1 / 62 (1.61%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Muscle necrosis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Osteitis                                        |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Osteoarthritis                                  |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Urinary tract infection                         |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 1 / 62 (1.61%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Appendicitis                                    |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Device related infection                        |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Erysipelas                                      |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 1 / 62 (1.61%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastroenteritis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Implant site infection                          |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Listeria sepsis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Osteomyelitis                                   |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urosepsis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Wound abscess                                   |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |                |                |                |
| Dehydration                                     |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 0 / 61 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypoglycaemia                                   |                |                |                |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 0 / 62 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

| Serious adverse events                                              | 200 mg - Double Dose | 300 mg - Double Dose |  |
|---------------------------------------------------------------------|----------------------|----------------------|--|
| Total subjects affected by serious adverse events                   |                      |                      |  |
| subjects affected / exposed                                         | 8 / 62 (12.90%)      | 9 / 61 (14.75%)      |  |
| number of deaths (all causes)                                       | 1                    | 0                    |  |
| number of deaths resulting from adverse events                      |                      |                      |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                      |                      |  |
| Hepatocellular carcinoma                                            |                      |                      |  |
| subjects affected / exposed                                         | 0 / 62 (0.00%)       | 0 / 61 (0.00%)       |  |
| occurrences causally related to treatment / all                     | 0 / 0                | 0 / 0                |  |
| deaths causally related to treatment / all                          | 0 / 0                | 0 / 0                |  |
| Prostate cancer                                                     |                      |                      |  |
| subjects affected / exposed                                         | 0 / 62 (0.00%)       | 0 / 61 (0.00%)       |  |
| occurrences causally related to treatment / all                     | 0 / 0                | 0 / 0                |  |
| deaths causally related to treatment / all                          | 0 / 0                | 0 / 0                |  |
| Squamous cell carcinoma of lung                                     |                      |                      |  |
| subjects affected / exposed                                         | 0 / 62 (0.00%)       | 0 / 61 (0.00%)       |  |
| occurrences causally related to treatment / all                     | 0 / 0                | 0 / 0                |  |
| deaths causally related to treatment / all                          | 0 / 0                | 0 / 0                |  |
| Tongue neoplasm malignant stage                                     |                      |                      |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Adenocarcinoma of colon                         |                |                |  |
| subjects affected / exposed                     | 1 / 62 (1.61%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Bladder cancer                                  |                |                |  |
| subjects affected / exposed                     | 1 / 62 (1.61%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Glioblastoma                                    |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 1 / 61 (1.64%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Intestinal adenocarcinoma                       |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 1 / 61 (1.64%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Bladder transitional cell carcinoma stage 0     |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 1 / 61 (1.64%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal tract adenoma                  |                |                |  |
| subjects affected / exposed                     | 1 / 62 (1.61%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Non-small cell lung cancer stage I              |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Oesophageal adenocarcinoma                      |                |                |  |

|                                                      |                |                |  |
|------------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                          | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Pituitary tumour benign                              |                |                |  |
| subjects affected / exposed                          | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Squamous cell carcinoma of skin                      |                |                |  |
| subjects affected / exposed                          | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Vascular disorders                                   |                |                |  |
| Aortic dissection                                    |                |                |  |
| subjects affected / exposed                          | 1 / 62 (1.61%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Hypotension                                          |                |                |  |
| subjects affected / exposed                          | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Orthostatic hypotension                              |                |                |  |
| subjects affected / exposed                          | 0 / 62 (0.00%) | 1 / 61 (1.64%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Intermittent claudication                            |                |                |  |
| subjects affected / exposed                          | 1 / 62 (1.61%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| General disorders and administration site conditions |                |                |  |
| Device dislocation                                   |                |                |  |
| subjects affected / exposed                          | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Pain                                            |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Non-cardiac chest pain                          |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Stent-graft endoleak                            |                |                |  |
| subjects affected / exposed                     | 1 / 62 (1.61%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Vascular stent restenosis                       |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Chronic obstructive pulmonary disease           |                |                |  |
| subjects affected / exposed                     | 1 / 62 (1.61%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Investigations                                  |                |                |  |
| Transaminases increased                         |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Haemoglobin decreased                           |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Platelet count decreased                        |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Injury, poisoning and procedural complications  |                |                |  |
| Concussion                                      |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Thoracic vertebral fracture                     |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Traumatic haemothorax                           |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Upper limb fracture                             |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Facial bones fracture                           |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Humerus fracture                                |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Intentional overdose                            |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Ligament sprain                                 |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 62 (1.61%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Post procedural complication                    |                |                |  |
| subjects affected / exposed                     | 2 / 62 (3.23%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Post procedural haemorrhage                     |                |                |  |
| subjects affected / exposed                     | 1 / 62 (1.61%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Weaning failure                                 |                |                |  |
| subjects affected / exposed                     | 1 / 62 (1.61%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Limb crushing injury                            |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Multiple injuries                               |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumothorax traumatic                          |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac disorders                               |                |                |  |
| Angina pectoris                                 |                |                |  |
| subjects affected / exposed                     | 2 / 62 (3.23%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Angina unstable                                 |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Myocardial infarction                           |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 1 / 61 (1.64%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Acute myocardial infarction                     |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 1 / 61 (1.64%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Atrial flutter                                  |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 1 / 61 (1.64%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Atrial tachycardia                              |                |                |  |
| subjects affected / exposed                     | 1 / 62 (1.61%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Atrioventricular block complete                 |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Coronary artery disease                         |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 2 / 61 (3.28%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Atrial fibrillation                             |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 1 / 61 (1.64%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac arrest                                  |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pericarditis                                    |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Ventricular extrasystoles                       |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Nervous system disorders                        |                |                |  |
| Carpal tunnel syndrome                          |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Ischaemic stroke                                |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Lacunar stroke                                  |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Neuropathy peripheral                           |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Spinal cord ischaemia                           |                |                |  |
| subjects affected / exposed                     | 1 / 62 (1.61%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Syncope                                         |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 62 (1.61%) | 1 / 61 (1.64%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Blood and lymphatic system disorders            |                |                |  |
| Anaemia                                         |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                      |                |                |  |
| Constipation                                    |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Inguinal hernia                                 |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Proctitis ulcerative                            |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Aorto-oesophageal fistula                       |                |                |  |
| subjects affected / exposed                     | 1 / 62 (1.61%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastritis                                       |                |                |  |
| subjects affected / exposed                     | 1 / 62 (1.61%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Rectal haemorrhage                              |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Large intestine polyp                           |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Volvulus                                        |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Vomiting                                        |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hepatobiliary disorders                         |                |                |  |
| Hepatic haemorrhage                             |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal and urinary disorders                     |                |                |  |
| Calculus urinary                                |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Acute kidney injury                             |                |                |  |
| subjects affected / exposed                     | 1 / 62 (1.61%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Stress urinary incontinence                     |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Musculoskeletal and connective tissue disorders |                |                |  |
| Muscle necrosis                                 |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Osteitis                                        |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Osteoarthritis                                  |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Urinary tract infection                         |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Appendicitis                                    |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Device related infection                        |                |                |  |
| subjects affected / exposed                     | 1 / 62 (1.61%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| Erysipelas                                      |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastroenteritis                                 |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Implant site infection                          |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Listeria sepsis                                 |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 62 (1.61%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Osteomyelitis</b>                            |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Urosepsis</b>                                |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 1 / 61 (1.64%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Wound abscess</b>                            |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Metabolism and nutrition disorders</b>       |                |                |  |
| <b>Dehydration</b>                              |                |                |  |
| subjects affected / exposed                     | 1 / 62 (1.61%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Hypoglycaemia</b>                            |                |                |  |
| subjects affected / exposed                     | 0 / 62 (0.00%) | 0 / 61 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | Placebo - Single Dose | 200 mg - Single Dose | 300 mg - Single Dose |
|-------------------------------------------------------|-----------------------|----------------------|----------------------|
| Total subjects affected by non-serious adverse events |                       |                      |                      |
| subjects affected / exposed                           | 50 / 65 (76.92%)      | 49 / 60 (81.67%)     | 49 / 61 (80.33%)     |
| <b>Investigations</b>                                 |                       |                      |                      |
| Blood creatine phosphokinase increased                |                       |                      |                      |
| subjects affected / exposed                           | 3 / 65 (4.62%)        | 1 / 60 (1.67%)       | 1 / 61 (1.64%)       |
| occurrences (all)                                     | 3                     | 1                    | 1                    |

|                                                      |                |                |                |
|------------------------------------------------------|----------------|----------------|----------------|
| Injury, poisoning and procedural complications       |                |                |                |
| Fall                                                 |                |                |                |
| subjects affected / exposed                          | 1 / 65 (1.54%) | 0 / 60 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all)                                    | 1              | 0              | 1              |
| Contusion                                            |                |                |                |
| subjects affected / exposed                          | 1 / 65 (1.54%) | 1 / 60 (1.67%) | 2 / 61 (3.28%) |
| occurrences (all)                                    | 1              | 1              | 2              |
| Vascular disorders                                   |                |                |                |
| Hypertension                                         |                |                |                |
| subjects affected / exposed                          | 0 / 65 (0.00%) | 2 / 60 (3.33%) | 3 / 61 (4.92%) |
| occurrences (all)                                    | 0              | 2              | 3              |
| Cardiac disorders                                    |                |                |                |
| Angina pectoris                                      |                |                |                |
| subjects affected / exposed                          | 1 / 65 (1.54%) | 2 / 60 (3.33%) | 4 / 61 (6.56%) |
| occurrences (all)                                    | 1              | 2              | 5              |
| Nervous system disorders                             |                |                |                |
| Dizziness                                            |                |                |                |
| subjects affected / exposed                          | 3 / 65 (4.62%) | 1 / 60 (1.67%) | 2 / 61 (3.28%) |
| occurrences (all)                                    | 4              | 1              | 2              |
| Headache                                             |                |                |                |
| subjects affected / exposed                          | 6 / 65 (9.23%) | 2 / 60 (3.33%) | 2 / 61 (3.28%) |
| occurrences (all)                                    | 6              | 2              | 2              |
| General disorders and administration site conditions |                |                |                |
| Fatigue                                              |                |                |                |
| subjects affected / exposed                          | 5 / 65 (7.69%) | 2 / 60 (3.33%) | 4 / 61 (6.56%) |
| occurrences (all)                                    | 7              | 2              | 4              |
| Gastrointestinal disorders                           |                |                |                |
| Constipation                                         |                |                |                |
| subjects affected / exposed                          | 1 / 65 (1.54%) | 4 / 60 (6.67%) | 2 / 61 (3.28%) |
| occurrences (all)                                    | 1              | 5              | 2              |
| Diarrhoea                                            |                |                |                |
| subjects affected / exposed                          | 1 / 65 (1.54%) | 1 / 60 (1.67%) | 4 / 61 (6.56%) |
| occurrences (all)                                    | 1              | 1              | 4              |
| Abdominal pain                                       |                |                |                |
| subjects affected / exposed                          | 2 / 65 (3.08%) | 3 / 60 (5.00%) | 2 / 61 (3.28%) |
| occurrences (all)                                    | 2              | 4              | 2              |
| Nausea                                               |                |                |                |

|                                                 |                |                 |                 |
|-------------------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 65 (3.08%) | 1 / 60 (1.67%)  | 1 / 61 (1.64%)  |
| occurrences (all)                               | 2              | 1               | 1               |
| Vomiting                                        |                |                 |                 |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 1 / 60 (1.67%)  | 2 / 61 (3.28%)  |
| occurrences (all)                               | 0              | 1               | 2               |
| Respiratory, thoracic and mediastinal disorders |                |                 |                 |
| Cough                                           |                |                 |                 |
| subjects affected / exposed                     | 2 / 65 (3.08%) | 4 / 60 (6.67%)  | 7 / 61 (11.48%) |
| occurrences (all)                               | 2              | 4               | 7               |
| Epistaxis                                       |                |                 |                 |
| subjects affected / exposed                     | 4 / 65 (6.15%) | 0 / 60 (0.00%)  | 0 / 61 (0.00%)  |
| occurrences (all)                               | 4              | 0               | 0               |
| Musculoskeletal and connective tissue disorders |                |                 |                 |
| Arthralgia                                      |                |                 |                 |
| subjects affected / exposed                     | 2 / 65 (3.08%) | 4 / 60 (6.67%)  | 4 / 61 (6.56%)  |
| occurrences (all)                               | 2              | 6               | 4               |
| Back pain                                       |                |                 |                 |
| subjects affected / exposed                     | 5 / 65 (7.69%) | 4 / 60 (6.67%)  | 4 / 61 (6.56%)  |
| occurrences (all)                               | 5              | 4               | 4               |
| Myalgia                                         |                |                 |                 |
| subjects affected / exposed                     | 3 / 65 (4.62%) | 2 / 60 (3.33%)  | 6 / 61 (9.84%)  |
| occurrences (all)                               | 4              | 2               | 7               |
| Musculoskeletal pain                            |                |                 |                 |
| subjects affected / exposed                     | 1 / 65 (1.54%) | 2 / 60 (3.33%)  | 0 / 61 (0.00%)  |
| occurrences (all)                               | 1              | 2               | 0               |
| Pain in extremity                               |                |                 |                 |
| subjects affected / exposed                     | 2 / 65 (3.08%) | 2 / 60 (3.33%)  | 1 / 61 (1.64%)  |
| occurrences (all)                               | 2              | 2               | 1               |
| Infections and infestations                     |                |                 |                 |
| Gastroenteritis                                 |                |                 |                 |
| subjects affected / exposed                     | 0 / 65 (0.00%) | 3 / 60 (5.00%)  | 2 / 61 (3.28%)  |
| occurrences (all)                               | 0              | 4               | 2               |
| Nasopharyngitis                                 |                |                 |                 |
| subjects affected / exposed                     | 4 / 65 (6.15%) | 8 / 60 (13.33%) | 9 / 61 (14.75%) |
| occurrences (all)                               | 4              | 13              | 12              |
| Urinary tract infection                         |                |                 |                 |

|                                   |                |                |                |
|-----------------------------------|----------------|----------------|----------------|
| subjects affected / exposed       | 1 / 65 (1.54%) | 1 / 60 (1.67%) | 5 / 61 (8.20%) |
| occurrences (all)                 | 1              | 1              | 10             |
| Influenza                         |                |                |                |
| subjects affected / exposed       | 3 / 65 (4.62%) | 3 / 60 (5.00%) | 4 / 61 (6.56%) |
| occurrences (all)                 | 3              | 3              | 4              |
| Upper respiratory tract infection |                |                |                |
| subjects affected / exposed       | 2 / 65 (3.08%) | 2 / 60 (3.33%) | 4 / 61 (6.56%) |
| occurrences (all)                 | 2              | 2              | 5              |

| <b>Non-serious adverse events</b>                     | 500 mg - Single Dose | Placebo - Double Dose | 100 mg - Double Dose |
|-------------------------------------------------------|----------------------|-----------------------|----------------------|
| Total subjects affected by non-serious adverse events |                      |                       |                      |
| subjects affected / exposed                           | 54 / 65 (83.08%)     | 51 / 62 (82.26%)      | 47 / 61 (77.05%)     |
| Investigations                                        |                      |                       |                      |
| Blood creatine phosphokinase increased                |                      |                       |                      |
| subjects affected / exposed                           | 0 / 65 (0.00%)       | 5 / 62 (8.06%)        | 0 / 61 (0.00%)       |
| occurrences (all)                                     | 0                    | 6                     | 0                    |
| Injury, poisoning and procedural complications        |                      |                       |                      |
| Fall                                                  |                      |                       |                      |
| subjects affected / exposed                           | 1 / 65 (1.54%)       | 1 / 62 (1.61%)        | 4 / 61 (6.56%)       |
| occurrences (all)                                     | 1                    | 1                     | 4                    |
| Contusion                                             |                      |                       |                      |
| subjects affected / exposed                           | 2 / 65 (3.08%)       | 5 / 62 (8.06%)        | 3 / 61 (4.92%)       |
| occurrences (all)                                     | 3                    | 5                     | 4                    |
| Vascular disorders                                    |                      |                       |                      |
| Hypertension                                          |                      |                       |                      |
| subjects affected / exposed                           | 1 / 65 (1.54%)       | 3 / 62 (4.84%)        | 4 / 61 (6.56%)       |
| occurrences (all)                                     | 1                    | 5                     | 4                    |
| Cardiac disorders                                     |                      |                       |                      |
| Angina pectoris                                       |                      |                       |                      |
| subjects affected / exposed                           | 1 / 65 (1.54%)       | 2 / 62 (3.23%)        | 0 / 61 (0.00%)       |
| occurrences (all)                                     | 1                    | 2                     | 0                    |
| Nervous system disorders                              |                      |                       |                      |
| Dizziness                                             |                      |                       |                      |
| subjects affected / exposed                           | 2 / 65 (3.08%)       | 6 / 62 (9.68%)        | 3 / 61 (4.92%)       |
| occurrences (all)                                     | 2                    | 8                     | 3                    |
| Headache                                              |                      |                       |                      |

|                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                 |                                                                                                                                 |                                                                                                                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                    | 2 / 65 (3.08%)<br>2                                                                                                             | 5 / 62 (8.06%)<br>7                                                                                                             | 5 / 61 (8.20%)<br>6                                                                                                             |
| General disorders and administration<br>site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                              | 2 / 65 (3.08%)<br>2                                                                                                             | 6 / 62 (9.68%)<br>7                                                                                                             | 2 / 61 (3.28%)<br>2                                                                                                             |
| Gastrointestinal disorders<br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Nausea<br>subjects affected / exposed<br>occurrences (all)<br><br>Vomiting<br>subjects affected / exposed<br>occurrences (all) | 1 / 65 (1.54%)<br>1<br><br>4 / 65 (6.15%)<br>5<br><br>0 / 65 (0.00%)<br>0<br><br>4 / 65 (6.15%)<br>4<br><br>1 / 65 (1.54%)<br>1 | 2 / 62 (3.23%)<br>2<br><br>2 / 62 (3.23%)<br>2<br><br>3 / 62 (4.84%)<br>3<br><br>3 / 62 (4.84%)<br>3<br><br>0 / 62 (0.00%)<br>0 | 0 / 61 (0.00%)<br>0<br><br>3 / 61 (4.92%)<br>3<br><br>2 / 61 (3.28%)<br>2<br><br>2 / 61 (3.28%)<br>2<br><br>0 / 61 (0.00%)<br>0 |
| Respiratory, thoracic and mediastinal<br>disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Epistaxis<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                | 3 / 65 (4.62%)<br>3<br><br>1 / 65 (1.54%)<br>1                                                                                  | 3 / 62 (4.84%)<br>3<br><br>1 / 62 (1.61%)<br>1                                                                                  | 1 / 61 (1.64%)<br>1<br><br>0 / 61 (0.00%)<br>0                                                                                  |
| Musculoskeletal and connective tissue<br>disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Back pain                                                                                                                                                                                                                                               | 4 / 65 (6.15%)<br>4                                                                                                             | 1 / 62 (1.61%)<br>1                                                                                                             | 2 / 61 (3.28%)<br>2                                                                                                             |

|                                                                                       |                       |                      |                       |
|---------------------------------------------------------------------------------------|-----------------------|----------------------|-----------------------|
| subjects affected / exposed<br>occurrences (all)                                      | 4 / 65 (6.15%)<br>4   | 2 / 62 (3.23%)<br>2  | 6 / 61 (9.84%)<br>6   |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                           | 3 / 65 (4.62%)<br>3   | 3 / 62 (4.84%)<br>3  | 7 / 61 (11.48%)<br>7  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)              | 1 / 65 (1.54%)<br>1   | 4 / 62 (6.45%)<br>5  | 0 / 61 (0.00%)<br>0   |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 65 (3.08%)<br>2   | 4 / 62 (6.45%)<br>4  | 1 / 61 (1.64%)<br>2   |
| <b>Infections and infestations</b>                                                    |                       |                      |                       |
| Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 65 (1.54%)<br>1   | 2 / 62 (3.23%)<br>2  | 3 / 61 (4.92%)<br>3   |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 9 / 65 (13.85%)<br>10 | 8 / 62 (12.90%)<br>9 | 8 / 61 (13.11%)<br>13 |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 0 / 65 (0.00%)<br>0   | 4 / 62 (6.45%)<br>4  | 1 / 61 (1.64%)<br>1   |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                         | 5 / 65 (7.69%)<br>5   | 2 / 62 (3.23%)<br>2  | 3 / 61 (4.92%)<br>4   |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 5 / 65 (7.69%)<br>6   | 2 / 62 (3.23%)<br>2  | 2 / 61 (3.28%)<br>3   |

| <b>Non-serious adverse events</b>                                                                               | 200 mg - Double<br>Dose | 300 mg - Double<br>Dose |  |
|-----------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed                         | 49 / 62 (79.03%)        | 51 / 61 (83.61%)        |  |
| Investigations<br>Blood creatine phosphokinase<br>increased<br>subjects affected / exposed<br>occurrences (all) | 3 / 62 (4.84%)<br>3     | 0 / 61 (0.00%)<br>0     |  |
| Injury, poisoning and procedural<br>complications                                                               |                         |                         |  |

|                                                                                                                                                                                                                                                             |                                                                            |                                                                           |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------|--|
| Fall<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                    | 1 / 62 (1.61%)<br>1                                                        | 0 / 61 (0.00%)<br>0                                                       |  |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                               | 1 / 62 (1.61%)<br>1                                                        | 2 / 61 (3.28%)<br>2                                                       |  |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                      | 2 / 62 (3.23%)<br>3                                                        | 1 / 61 (1.64%)<br>1                                                       |  |
| Cardiac disorders<br>Angina pectoris<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                    | 2 / 62 (3.23%)<br>2                                                        | 0 / 61 (0.00%)<br>0                                                       |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all)                                                                                               | 3 / 62 (4.84%)<br>3<br><br>1 / 62 (1.61%)<br>1                             | 3 / 61 (4.92%)<br>3<br><br>5 / 61 (8.20%)<br>6                            |  |
| General disorders and administration<br>site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                      | 0 / 62 (0.00%)<br>0                                                        | 1 / 61 (1.64%)<br>1                                                       |  |
| Gastrointestinal disorders<br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Nausea | 2 / 62 (3.23%)<br>2<br><br>7 / 62 (11.29%)<br>7<br><br>1 / 62 (1.61%)<br>1 | 1 / 61 (1.64%)<br>1<br><br>5 / 61 (8.20%)<br>6<br><br>4 / 61 (6.56%)<br>5 |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                            |                                                                                                                                                            |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                                                                                                                                                                                                                                                                                                   | <p>4 / 62 (6.45%)</p> <p>4</p> <p>4 / 62 (6.45%)</p> <p>4</p>                                                                                              | <p>3 / 61 (4.92%)</p> <p>3</p> <p>0 / 61 (0.00%)</p> <p>0</p>                                                                                              |  |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Epistaxis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                                                                                                                                                                                                                              | <p>6 / 62 (9.68%)</p> <p>6</p> <p>1 / 62 (1.61%)</p> <p>1</p>                                                                                              | <p>3 / 61 (4.92%)</p> <p>3</p> <p>0 / 61 (0.00%)</p> <p>0</p>                                                                                              |  |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Myalgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Musculoskeletal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain in extremity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>5 / 62 (8.06%)</p> <p>5</p> <p>1 / 62 (1.61%)</p> <p>1</p> <p>5 / 62 (8.06%)</p> <p>5</p> <p>0 / 62 (0.00%)</p> <p>0</p> <p>4 / 62 (6.45%)</p> <p>5</p> | <p>3 / 61 (4.92%)</p> <p>3</p> <p>4 / 61 (6.56%)</p> <p>5</p> <p>5 / 61 (8.20%)</p> <p>8</p> <p>6 / 61 (9.84%)</p> <p>6</p> <p>1 / 61 (1.64%)</p> <p>1</p> |  |
| <p>Infections and infestations</p> <p>Gastroenteritis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nasopharyngitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Urinary tract infection</p>                                                                                                                                                                                                                                   | <p>1 / 62 (1.61%)</p> <p>1</p> <p>5 / 62 (8.06%)</p> <p>5</p>                                                                                              | <p>1 / 61 (1.64%)</p> <p>1</p> <p>11 / 61 (18.03%)</p> <p>12</p>                                                                                           |  |

|                                   |                |                |  |
|-----------------------------------|----------------|----------------|--|
| subjects affected / exposed       | 1 / 62 (1.61%) | 2 / 61 (3.28%) |  |
| occurrences (all)                 | 2              | 2              |  |
| Influenza                         |                |                |  |
| subjects affected / exposed       | 4 / 62 (6.45%) | 5 / 61 (8.20%) |  |
| occurrences (all)                 | 4              | 5              |  |
| Upper respiratory tract infection |                |                |  |
| subjects affected / exposed       | 1 / 62 (1.61%) | 3 / 61 (4.92%) |  |
| occurrences (all)                 | 1              | 4              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 11 January 2016 | <ul style="list-style-type: none"><li>• Addition of an interim analysis of lipids and PCSK9 at Day 90. Addition of a secondary endpoint for LDL-C levels at Day 90</li><li>• The exploratory objective has been re-worded to provide a more specific description of the event terms that will be reported</li><li>• Any participants in whom LDL-C levels have not returned to &gt;80% of baseline values will continue to be followed-up monthly as part of this study until either this level has been reached or until Day 360. Additional follow-up visits added to schedule</li><li>• Anti-drug antibodies will be assessed when LDL-C returns to &gt;80% baseline or at Day 360</li><li>• Amended exclusion criterion 11 to state that contraception must be used during the entire study period</li><li>• Additional exclusion criterion 17 to exclude participants that have received monoclonal antibodies directed towards PCSK9</li><li>• Additional description of sample size calculation and statistical methods</li><li>• Removal of description of the open-label extension study</li><li>• Neurological examination added as part of the physical examination</li><li>• Addition of monthly pregnancy test for women of childbearing potential</li><li>• Addition of Sampson Criteria for diagnosing anaphylaxis</li></ul> |
| 18 March 2016   | <ul style="list-style-type: none"><li>• Additional anti-drug antibody assessments at Day 60 and Day 90 (and at Day 150 and Day 180 in participants that received a second dose).</li><li>• Addition of reference to the open-label extension study</li><li>• Additional information on completed in vitro and in vivo non-clinical studies</li><li>• Specify that height and weight to be recorded as part of the physical examination</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 12 April 2016   | <ul style="list-style-type: none"><li>• Amended exclusion criterion 13 to exclude participants with a history of alcohol / drug abuse within the last five years</li><li>• Amended exclusion criteria 17 to clarify that participants should not have received monoclonal antibodies directed towards PCSK9 within 90 days of screening</li><li>• Specified that abnormal neurological examination or anaphylactic reaction must be recorded on the source documentation and the electronic case report form</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported