



## Clinical trial results:

### A Global, Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of BMS-986177, an Oral Factor XIa Inhibitor, for the Prevention of New Ischemic Stroke or New Covert Brain Infarction in Patients Receiving Aspirin and Clopidogrel Following Acute Ischemic Stroke or Transient Ischemic Attack (TIA)

#### Summary

|                          |                                        |
|--------------------------|----------------------------------------|
| EudraCT number           | 2017-005029-19                         |
| Trial protocol           | CZ DE ES SE HU NO FI BE GB AT DK GR IT |
| Global end of trial date | 31 March 2022                          |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1            |
| This version publication date  | 17 April 2023 |
| First version publication date | 17 April 2023 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | CV010-031 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03766581 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                                 |
|------------------------------|-------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Bristol-Myers Squibb                                                                            |
| Sponsor organisation address | Chaussee de la Hulpe 185, Brussels, Belgium, 1170                                               |
| Public contact               | EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com |
| Scientific contact           | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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                       | 13 May 2022   |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 31 March 2022 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this clinical study is to estimate the dose-response relationship of milvexian in participants with ischemic stroke or transient ischemic attack (TIA) treated with aspirin and clopidogrel.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment                          | 27 January 2019 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 23          |
| Country: Number of subjects enrolled | Australia: 49          |
| Country: Number of subjects enrolled | Austria: 12            |
| Country: Number of subjects enrolled | Belgium: 55            |
| Country: Number of subjects enrolled | Brazil: 41             |
| Country: Number of subjects enrolled | Canada: 126            |
| Country: Number of subjects enrolled | Chile: 4               |
| Country: Number of subjects enrolled | Czechia: 13            |
| Country: Number of subjects enrolled | Denmark: 43            |
| Country: Number of subjects enrolled | Finland: 33            |
| Country: Number of subjects enrolled | France: 104            |
| Country: Number of subjects enrolled | Germany: 100           |
| Country: Number of subjects enrolled | Greece: 211            |
| Country: Number of subjects enrolled | Hungary: 221           |
| Country: Number of subjects enrolled | Israel: 64             |
| Country: Number of subjects enrolled | Italy: 56              |
| Country: Number of subjects enrolled | Japan: 295             |
| Country: Number of subjects enrolled | Korea, Republic of: 91 |
| Country: Number of subjects enrolled | Mexico: 1              |
| Country: Number of subjects enrolled | Norway: 10             |

|                                      |                       |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Poland: 160           |
| Country: Number of subjects enrolled | Russian Federation: 9 |
| Country: Number of subjects enrolled | Spain: 342            |
| Country: Number of subjects enrolled | Sweden: 27            |
| Country: Number of subjects enrolled | Switzerland: 25       |
| Country: Number of subjects enrolled | United Kingdom: 39    |
| Country: Number of subjects enrolled | United States: 212    |
| Worldwide total number of subjects   | 2366                  |
| EEA total number of subjects         | 1387                  |

Notes:

| <b>Subjects enrolled per age group</b>    |      |
|-------------------------------------------|------|
| In utero                                  | 0    |
| Preterm newborn - gestational age < 37 wk | 0    |
| Newborns (0-27 days)                      | 0    |
| Infants and toddlers (28 days-23 months)  | 0    |
| Children (2-11 years)                     | 0    |
| Adolescents (12-17 years)                 | 0    |
| Adults (18-64 years)                      | 720  |
| From 65 to 84 years                       | 1481 |
| 85 years and over                         | 165  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

2366 participants were randomized and 2334 treated. 1 participant was randomized to Milvexian 200 mg BID, but received Milvexian 25 mg QD.

### Period 1

|                              |                         |
|------------------------------|-------------------------|
| Period 1 title               | Randomization           |
| Is this the baseline period? | Yes                     |
| Allocation method            | Randomised - controlled |
| Blinding used                | Double blind            |
| Roles blinded                | Subject, Investigator   |

### Arms

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

Arm description:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Placebo + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Placebo + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |             |
|----------------------------------------|-------------|
| Arm type                               | Placebo     |
| Investigational medicinal product name | Clopidogrel |
| Investigational medicinal product code |             |
| Other name                             |             |
| Pharmaceutical forms                   | Tablet      |
| Routes of administration               | Oral use    |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Placebo + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Placebo + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |          |
|----------------------------------------|----------|
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Placebo + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Placebo + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |          |
|----------------------------------------|----------|
| Investigational medicinal product name | Aspirin  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Placebo + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Placebo + Aspirin 100 mg QD on days 22-90. All administered orally.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Milvexian 25 mg QD |
|------------------|--------------------|

**Arm description:**

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Clopidogrel  |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

**Dosage and administration details:**

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |           |
|----------------------------------------|-----------|
| Investigational medicinal product name | Milvexian |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

**Dosage and administration details:**

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |          |
|----------------------------------------|----------|
| Investigational medicinal product name | Aspirin  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

**Dosage and administration details:**

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | Milvexian 25 mg BID |
|------------------|---------------------|

**Arm description:**

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Clopidogrel  |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

**Dosage and administration details:**

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |           |
|----------------------------------------|-----------|
| Investigational medicinal product name | Milvexian |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

**Dosage and administration details:**

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg BID + Aspirin 100 mg QD on days

22-90. All administered orally.

|                                        |          |
|----------------------------------------|----------|
| Investigational medicinal product name | Aspirin  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | Milvexian 50 mg BID |
|------------------|---------------------|

Arm description:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Clopidogrel  |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |           |
|----------------------------------------|-----------|
| Investigational medicinal product name | Milvexian |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |          |
|----------------------------------------|----------|
| Investigational medicinal product name | Aspirin  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | Milvexian 100 mg BID |
|------------------|----------------------|

Arm description:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Clopidogrel  |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |           |
|----------------------------------------|-----------|
| Investigational medicinal product name | Milvexian |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |          |
|----------------------------------------|----------|
| Investigational medicinal product name | Aspirin  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | Milvexian 200 mg BID |
|------------------|----------------------|

Arm description:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 200 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 200 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Clopidogrel  |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 200 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 200 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |          |
|----------------------------------------|----------|
| Investigational medicinal product name | Aspirin  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 200 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 200 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |           |
|----------------------------------------|-----------|
| Investigational medicinal product name | Milvexian |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 200 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 200 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                                                                                                                                                                                                                                                       |                     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| <b>Arm title</b>                                                                                                                                                                                                                                                      | Milvexian 50 mg QD  |
| Arm description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.                     |                     |
| Arm type                                                                                                                                                                                                                                                              | Experimental        |
| Investigational medicinal product name                                                                                                                                                                                                                                | Clopidogrel         |
| Investigational medicinal product code                                                                                                                                                                                                                                |                     |
| Other name                                                                                                                                                                                                                                                            |                     |
| Pharmaceutical forms                                                                                                                                                                                                                                                  | Tablet              |
| Routes of administration                                                                                                                                                                                                                                              | Oral use            |
| Dosage and administration details:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.   |                     |
| Investigational medicinal product name                                                                                                                                                                                                                                | Milvexian           |
| Investigational medicinal product code                                                                                                                                                                                                                                |                     |
| Other name                                                                                                                                                                                                                                                            |                     |
| Pharmaceutical forms                                                                                                                                                                                                                                                  | Tablet              |
| Routes of administration                                                                                                                                                                                                                                              | Oral use            |
| Dosage and administration details:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.   |                     |
| Investigational medicinal product name                                                                                                                                                                                                                                | Aspirin             |
| Investigational medicinal product code                                                                                                                                                                                                                                |                     |
| Other name                                                                                                                                                                                                                                                            |                     |
| Pharmaceutical forms                                                                                                                                                                                                                                                  | Tablet              |
| Routes of administration                                                                                                                                                                                                                                              | Oral use            |
| Dosage and administration details:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.   |                     |
| <b>Arm title</b>                                                                                                                                                                                                                                                      | Milvexian 100 mg QD |
| Arm description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.                   |                     |
| Arm type                                                                                                                                                                                                                                                              | Experimental        |
| Investigational medicinal product name                                                                                                                                                                                                                                | Clopidogrel         |
| Investigational medicinal product code                                                                                                                                                                                                                                |                     |
| Other name                                                                                                                                                                                                                                                            |                     |
| Pharmaceutical forms                                                                                                                                                                                                                                                  | Tablet              |
| Routes of administration                                                                                                                                                                                                                                              | Oral use            |
| Dosage and administration details:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally. |                     |
| Investigational medicinal product name                                                                                                                                                                                                                                | Milvexian           |
| Investigational medicinal product code                                                                                                                                                                                                                                |                     |
| Other name                                                                                                                                                                                                                                                            |                     |
| Pharmaceutical forms                                                                                                                                                                                                                                                  | Tablet              |
| Routes of administration                                                                                                                                                                                                                                              | Oral use            |
| Dosage and administration details:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally. |                     |



mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |          |
|----------------------------------------|----------|
| Investigational medicinal product name | Aspirin  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.

| Number of subjects in period 1                     | Placebo | Milvexian 25 mg QD | Milvexian 25 mg BID |
|----------------------------------------------------|---------|--------------------|---------------------|
| Started                                            | 691     | 328                | 318                 |
| Completed                                          | 682     | 324                | 313                 |
| Not completed                                      | 9       | 4                  | 5                   |
| Participant withdrew consent                       | 1       | -                  | 1                   |
| Participant no longer meets study criteria         | 5       | 3                  | 4                   |
| Other reasons                                      | 2       | 1                  | -                   |
| Participant request to discontinue study treatment | 1       | -                  | -                   |

| Number of subjects in period 1                     | Milvexian 50 mg BID | Milvexian 100 mg BID | Milvexian 200 mg BID |
|----------------------------------------------------|---------------------|----------------------|----------------------|
| Started                                            | 328                 | 310                  | 351                  |
| Completed                                          | 325                 | 306                  | 345                  |
| Not completed                                      | 3                   | 4                    | 6                    |
| Participant withdrew consent                       | 2                   | 1                    | 1                    |
| Participant no longer meets study criteria         | -                   | 2                    | 3                    |
| Other reasons                                      | 1                   | -                    | -                    |
| Participant request to discontinue study treatment | -                   | 1                    | 2                    |

| Number of subjects in period 1                     | Milvexian 50 mg QD | Milvexian 100 mg QD |
|----------------------------------------------------|--------------------|---------------------|
| Started                                            | 22                 | 18                  |
| Completed                                          | 22                 | 17                  |
| Not completed                                      | 0                  | 1                   |
| Participant withdrew consent                       | -                  | -                   |
| Participant no longer meets study criteria         | -                  | 1                   |
| Other reasons                                      | -                  | -                   |
| Participant request to discontinue study treatment | -                  | -                   |

## Period 2

|                              |                         |
|------------------------------|-------------------------|
| Period 2 title               | Treatment               |
| Is this the baseline period? | No                      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Double blind            |
| Roles blinded                | Subject, Investigator   |

## Arms

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

### Arm description:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Placebo + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Placebo + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |             |
|----------------------------------------|-------------|
| Arm type                               | Placebo     |
| Investigational medicinal product name | Clopidogrel |
| Investigational medicinal product code |             |
| Other name                             |             |
| Pharmaceutical forms                   | Tablet      |
| Routes of administration               | Oral use    |

### Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Placebo + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Placebo + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |          |
|----------------------------------------|----------|
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

### Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Placebo + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Placebo + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |          |
|----------------------------------------|----------|
| Investigational medicinal product name | Aspirin  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

### Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Placebo + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Placebo + Aspirin 100 mg QD on days 22-90. All administered orally.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Milvexian 25 mg QD |
|------------------|--------------------|

### Arm description:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.

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

|                                        |             |
|----------------------------------------|-------------|
| Investigational medicinal product name | Clopidogrel |
| Investigational medicinal product code |             |
| Other name                             |             |
| Pharmaceutical forms                   | Tablet      |
| Routes of administration               | Oral use    |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |           |
|----------------------------------------|-----------|
| Investigational medicinal product name | Milvexian |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |          |
|----------------------------------------|----------|
| Investigational medicinal product name | Aspirin  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | Milvexian 25 mg BID |
|------------------|---------------------|

Arm description:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Clopidogrel  |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |           |
|----------------------------------------|-----------|
| Investigational medicinal product name | Milvexian |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |         |
|----------------------------------------|---------|
| Investigational medicinal product name | Aspirin |
| Investigational medicinal product code |         |
| Other name                             |         |
| Pharmaceutical forms                   | Tablet  |

|                          |          |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | Milvexian 50 mg BID |
|------------------|---------------------|

Arm description:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Clopidogrel  |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |           |
|----------------------------------------|-----------|
| Investigational medicinal product name | Milvexian |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |          |
|----------------------------------------|----------|
| Investigational medicinal product name | Aspirin  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | Milvexian 100 mg BID |
|------------------|----------------------|

Arm description:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Clopidogrel  |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |           |
|----------------------------------------|-----------|
| Investigational medicinal product name | Milvexian |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |          |
|----------------------------------------|----------|
| Investigational medicinal product name | Aspirin  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | Milvexian 200 mg BID |
|------------------|----------------------|

Arm description:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 200 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 200 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Clopidogrel  |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 200 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 200 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |           |
|----------------------------------------|-----------|
| Investigational medicinal product name | Milvexian |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 200 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 200 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |          |
|----------------------------------------|----------|
| Investigational medicinal product name | Aspirin  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 200 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 200 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Milvexian 50 mg QD |
|------------------|--------------------|

Arm description:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.

22-90. All administered orally.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Clopidogrel  |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |           |
|----------------------------------------|-----------|
| Investigational medicinal product name | Milvexian |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |          |
|----------------------------------------|----------|
| Investigational medicinal product name | Aspirin  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | Milvexian 100 mg QD |
|------------------|---------------------|

Arm description:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Clopidogrel  |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |           |
|----------------------------------------|-----------|
| Investigational medicinal product name | Milvexian |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.

|                                        |          |
|----------------------------------------|----------|
| Investigational medicinal product name | Aspirin  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.

| Number of subjects in period 2               | Placebo | Milvexian 25 mg QD | Milvexian 25 mg BID |
|----------------------------------------------|---------|--------------------|---------------------|
| Started                                      | 682     | 325                | 313                 |
| Completed                                    | 529     | 260                | 242                 |
| Not completed                                | 153     | 65                 | 71                  |
| Adverse event, serious fatal                 | 1       | -                  | -                   |
| Participant request to discontinue treatment | 34      | 6                  | 10                  |
| Participant withdrew consent                 | 11      | 4                  | 5                   |
| Poor/Non compliance                          | 2       | 2                  | 1                   |
| Adverse event, non-fatal                     | 82      | 44                 | 47                  |
| Participant no longer meets study criteria   | 9       | 1                  | 5                   |
| Other reasons                                | 13      | 8                  | 3                   |
| Lost to follow-up                            | 1       | -                  | -                   |

| Number of subjects in period 2               | Milvexian 50 mg BID | Milvexian 100 mg BID | Milvexian 200 mg BID |
|----------------------------------------------|---------------------|----------------------|----------------------|
| Started                                      | 325                 | 306                  | 344                  |
| Completed                                    | 251                 | 230                  | 240                  |
| Not completed                                | 74                  | 76                   | 104                  |
| Adverse event, serious fatal                 | -                   | -                    | -                    |
| Participant request to discontinue treatment | 10                  | 14                   | 15                   |
| Participant withdrew consent                 | 5                   | 4                    | 4                    |
| Poor/Non compliance                          | 1                   | 1                    | 1                    |
| Adverse event, non-fatal                     | 46                  | 50                   | 77                   |
| Participant no longer meets study criteria   | 4                   | 4                    | 4                    |
| Other reasons                                | 7                   | 3                    | 3                    |
| Lost to follow-up                            | 1                   | -                    | -                    |

| Number of subjects in period 2 | Milvexian 50 mg QD | Milvexian 100 mg QD |
|--------------------------------|--------------------|---------------------|
| Started                        | 22                 | 17                  |
| Completed                      | 15                 | 14                  |
| Not completed                  | 7                  | 3                   |

|                                              |   |   |
|----------------------------------------------|---|---|
| Adverse event, serious fatal                 | - | - |
| Participant request to discontinue treatment | - | 1 |
| Participant withdrew consent                 | - | - |
| Poor/Non compliance                          | - | - |
| Adverse event, non-fatal                     | 5 | 2 |
| Participant no longer meets study criteria   | 2 | - |
| Other reasons                                | - | - |
| Lost to follow-up                            | - | - |



## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                   |                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| Reporting group title                                                                                                                                                                                                                                             | Placebo              |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Placebo + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Placebo + Aspirin 100 mg QD on days 22-90. All administered orally.                           |                      |
| Reporting group title                                                                                                                                                                                                                                             | Milvexian 25 mg QD   |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.     |                      |
| Reporting group title                                                                                                                                                                                                                                             | Milvexian 25 mg BID  |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.   |                      |
| Reporting group title                                                                                                                                                                                                                                             | Milvexian 50 mg BID  |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.   |                      |
| Reporting group title                                                                                                                                                                                                                                             | Milvexian 100 mg BID |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally. |                      |
| Reporting group title                                                                                                                                                                                                                                             | Milvexian 200 mg BID |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 200 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 200 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally. |                      |
| Reporting group title                                                                                                                                                                                                                                             | Milvexian 50 mg QD   |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.     |                      |
| Reporting group title                                                                                                                                                                                                                                             | Milvexian 100 mg QD  |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.   |                      |

| Reporting group values                                | Placebo | Milvexian 25 mg QD | Milvexian 25 mg BID |
|-------------------------------------------------------|---------|--------------------|---------------------|
| Number of subjects                                    | 691     | 328                | 318                 |
| Age categorical<br>Units: Subjects                    |         |                    |                     |
| In utero                                              | 0       | 0                  | 0                   |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0       | 0                  | 0                   |
| Newborns (0-27 days)                                  | 0       | 0                  | 0                   |
| Infants and toddlers (28 days-23 months)              | 0       | 0                  | 0                   |

|                                           |         |         |         |
|-------------------------------------------|---------|---------|---------|
| Children (2-11 years)                     | 0       | 0       | 0       |
| Adolescents (12-17 years)                 | 0       | 0       | 0       |
| Adults (18-64 years)                      | 208     | 90      | 97      |
| From 65-84 years                          | 441     | 208     | 193     |
| 85 years and over                         | 42      | 30      | 28      |
| Age Continuous                            |         |         |         |
| Units: Years                              |         |         |         |
| arithmetic mean                           | 69.1    | 70.9    | 70.1    |
| standard deviation                        | ± 10.58 | ± 10.66 | ± 11.34 |
| Sex: Female, Male                         |         |         |         |
| Units:                                    |         |         |         |
| Female                                    | 254     | 109     | 118     |
| Male                                      | 437     | 219     | 200     |
| Ethnicity (NIH/OMB)                       |         |         |         |
| Units: Subjects                           |         |         |         |
| Hispanic or Latino                        | 10      | 4       | 2       |
| Not Hispanic or Latino                    | 62      | 20      | 22      |
| Unknown or Not Reported                   | 619     | 304     | 294     |
| Race/Ethnicity, Customized                |         |         |         |
| Race                                      |         |         |         |
| Units: Subjects                           |         |         |         |
| White                                     | 549     | 257     | 246     |
| Black or African American                 | 15      | 5       | 6       |
| Asian                                     | 35      | 12      | 21      |
| Native Hawaiian or Other Pacific Islander | 0       | 1       | 1       |
| Asian Indian                              | 2       | 1       | 2       |
| Chinese                                   | 0       | 0       | 0       |
| Japanese                                  | 84      | 46      | 40      |
| Malay                                     | 1       | 0       | 0       |
| Asian Other                               | 0       | 0       | 0       |
| Other                                     | 5       | 6       | 2       |

| Reporting group values                             | Milvexian 50 mg BID | Milvexian 100 mg BID | Milvexian 200 mg BID |
|----------------------------------------------------|---------------------|----------------------|----------------------|
| Number of subjects                                 | 328                 | 310                  | 351                  |
| Age categorical                                    |                     |                      |                      |
| Units: Subjects                                    |                     |                      |                      |
| In utero                                           | 0                   | 0                    | 0                    |
| Preterm newborn infants (gestational age < 37 wks) | 0                   | 0                    | 0                    |
| Newborns (0-27 days)                               | 0                   | 0                    | 0                    |
| Infants and toddlers (28 days-23 months)           | 0                   | 0                    | 0                    |
| Children (2-11 years)                              | 0                   | 0                    | 0                    |
| Adolescents (12-17 years)                          | 0                   | 0                    | 0                    |
| Adults (18-64 years)                               | 108                 | 92                   | 106                  |
| From 65-84 years                                   | 201                 | 198                  | 221                  |
| 85 years and over                                  | 19                  | 20                   | 24                   |
| Age Continuous                                     |                     |                      |                      |
| Units: Years                                       |                     |                      |                      |
| arithmetic mean                                    | 69.3                | 69.7                 | 69.5                 |
| standard deviation                                 | ± 10.69             | ± 10.59              | ± 11.11              |

|                                           |     |     |     |
|-------------------------------------------|-----|-----|-----|
| Sex: Female, Male                         |     |     |     |
| Units:                                    |     |     |     |
| Female                                    | 121 | 112 | 128 |
| Male                                      | 207 | 198 | 223 |
| Ethnicity (NIH/OMB)                       |     |     |     |
| Units: Subjects                           |     |     |     |
| Hispanic or Latino                        | 1   | 2   | 1   |
| Not Hispanic or Latino                    | 23  | 29  | 27  |
| Unknown or Not Reported                   | 304 | 279 | 323 |
| Race/Ethnicity, Customized                |     |     |     |
| Race                                      |     |     |     |
| Units: Subjects                           |     |     |     |
| White                                     | 260 | 251 | 288 |
| Black or African American                 | 8   | 3   | 5   |
| Asian                                     | 13  | 11  | 17  |
| Native Hawaiian or Other Pacific Islander | 0   | 0   | 0   |
| Asian Indian                              | 1   | 0   | 0   |
| Chinese                                   | 0   | 1   | 0   |
| Japanese                                  | 41  | 39  | 40  |
| Malay                                     | 0   | 0   | 0   |
| Asian Other                               | 1   | 0   | 0   |
| Other                                     | 4   | 5   | 1   |

| Reporting group values                             | Milvexian 50 mg QD | Milvexian 100 mg QD | Total |
|----------------------------------------------------|--------------------|---------------------|-------|
| Number of subjects                                 | 22                 | 18                  | 2366  |
| Age categorical                                    |                    |                     |       |
| Units: Subjects                                    |                    |                     |       |
| In utero                                           | 0                  | 0                   | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0                  | 0                   | 0     |
| Newborns (0-27 days)                               | 0                  | 0                   | 0     |
| Infants and toddlers (28 days-23 months)           | 0                  | 0                   | 0     |
| Children (2-11 years)                              | 0                  | 0                   | 0     |
| Adolescents (12-17 years)                          | 0                  | 0                   | 0     |
| Adults (18-64 years)                               | 10                 | 9                   | 720   |
| From 65-84 years                                   | 11                 | 8                   | 1481  |
| 85 years and over                                  | 1                  | 1                   | 165   |
| Age Continuous                                     |                    |                     |       |
| Units: Years                                       |                    |                     |       |
| arithmetic mean                                    | 65.7               | 65.4                |       |
| standard deviation                                 | ± 10.64            | ± 11.65             | -     |
| Sex: Female, Male                                  |                    |                     |       |
| Units:                                             |                    |                     |       |
| Female                                             | 7                  | 10                  | 859   |
| Male                                               | 15                 | 8                   | 1507  |
| Ethnicity (NIH/OMB)                                |                    |                     |       |
| Units: Subjects                                    |                    |                     |       |
| Hispanic or Latino                                 | 1                  | 1                   | 22    |
| Not Hispanic or Latino                             | 7                  | 7                   | 197   |
| Unknown or Not Reported                            | 14                 | 10                  | 2147  |

| Race/Ethnicity, Customized                |    |    |      |
|-------------------------------------------|----|----|------|
| Race                                      |    |    |      |
| Units: Subjects                           |    |    |      |
| White                                     | 18 | 15 | 1884 |
| Black or African American                 | 3  | 3  | 48   |
| Asian                                     | 0  | 0  | 109  |
| Native Hawaiian or Other Pacific Islander | 0  | 0  | 2    |
| Asian Indian                              | 0  | 0  | 6    |
| Chinese                                   | 0  | 0  | 1    |
| Japanese                                  | 0  | 0  | 290  |
| Malay                                     | 0  | 0  | 1    |
| Asian Other                               | 0  | 0  | 1    |
| Other                                     | 1  | 0  | 24   |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                   |                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| Reporting group title                                                                                                                                                                                                                                             | Placebo              |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Placebo + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Placebo + Aspirin 100 mg QD on days 22-90. All administered orally.                           |                      |
| Reporting group title                                                                                                                                                                                                                                             | Milvexian 25 mg QD   |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.     |                      |
| Reporting group title                                                                                                                                                                                                                                             | Milvexian 25 mg BID  |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.   |                      |
| Reporting group title                                                                                                                                                                                                                                             | Milvexian 50 mg BID  |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.   |                      |
| Reporting group title                                                                                                                                                                                                                                             | Milvexian 100 mg BID |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally. |                      |
| Reporting group title                                                                                                                                                                                                                                             | Milvexian 200 mg BID |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 200 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 200 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally. |                      |
| Reporting group title                                                                                                                                                                                                                                             | Milvexian 50 mg QD   |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.     |                      |
| Reporting group title                                                                                                                                                                                                                                             | Milvexian 100 mg QD  |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.   |                      |
| Reporting group title                                                                                                                                                                                                                                             | Placebo              |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Placebo + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Placebo + Aspirin 100 mg QD on days 22-90. All administered orally.                           |                      |
| Reporting group title                                                                                                                                                                                                                                             | Milvexian 25 mg QD   |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.     |                      |
| Reporting group title                                                                                                                                                                                                                                             | Milvexian 25 mg BID  |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.   |                      |

22-90. All administered orally.

|                                                                                                                                                                                                                                                                   |                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| Reporting group title                                                                                                                                                                                                                                             | Milvexian 50 mg BID  |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.   |                      |
| Reporting group title                                                                                                                                                                                                                                             | Milvexian 100 mg BID |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally. |                      |
| Reporting group title                                                                                                                                                                                                                                             | Milvexian 200 mg BID |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 200 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 200 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally. |                      |
| Reporting group title                                                                                                                                                                                                                                             | Milvexian 50 mg QD   |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.     |                      |
| Reporting group title                                                                                                                                                                                                                                             | Milvexian 100 mg QD  |
| Reporting group description:<br>Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.   |                      |

### **Primary: Percent of Participants with Model Based Assessment of Composite of New Ischemic Stroke During Treatment and New Covert Brain Infarction (FLAIR + DWI) Detected by MRI by Day 90**

|                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                   | Percent of Participants with Model Based Assessment of Composite of New Ischemic Stroke During Treatment and New Covert Brain Infarction (FLAIR + DWI) Detected by MRI by Day 90 <sup>[1]</sup> |
| End point description:<br>Model based assessment estimate for composite event is a customized statistical analysis called MCP-MOD (Multiple Comparison Procedures, MODel) estimation, which is used to check for dose-response relationship. 95% confidence interval (CI) for composite event based on bootstrap (10000 samples). |                                                                                                                                                                                                 |
| End point type                                                                                                                                                                                                                                                                                                                    | Primary                                                                                                                                                                                         |
| End point timeframe:<br>From randomization to up to 90 days after randomization                                                                                                                                                                                                                                                   |                                                                                                                                                                                                 |

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Endpoints are cohort specific and do not report for all arms.

| End point values                  | Placebo             | Milvexian 25 mg QD  | Milvexian 25 mg BID | Milvexian 50 mg BID |
|-----------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type                | Reporting group     | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed       | 625                 | 308                 | 287                 | 306                 |
| Units: Percentage of participants |                     |                     |                     |                     |
| number (confidence interval 95%)  | 16.8 (14.2 to 19.4) | 16.7 (14.4 to 19.0) | 16.6 (14.5 to 18.7) | 15.6 (13.6 to 17.9) |

| <b>End point values</b>           | Milvexian 100 mg BID | Milvexian 200 mg BID |  |  |
|-----------------------------------|----------------------|----------------------|--|--|
| Subject group type                | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed       | 277                  | 317                  |  |  |
| Units: Percentage of participants |                      |                      |  |  |
| number (confidence interval 95%)  | 15.4 (13.0 to 18.0)  | 15.3 (12.3 to 20.4)  |  |  |

## Statistical analyses

| <b>Statistical analysis title</b>                                                                                                                                          | Milvexian 25 mg QD over Placebo |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Statistical analysis description:<br>Multiple Comparison Procedures, MODel (MCP-MOD). 95% confidence interval (CI) for composite event based on bootstrap (10000 samples). |                                 |
| Comparison groups                                                                                                                                                          | Placebo v Milvexian 25 mg QD    |
| Number of subjects included in analysis                                                                                                                                    | 933                             |
| Analysis specification                                                                                                                                                     | Pre-specified                   |
| Analysis type                                                                                                                                                              | superiority                     |
| Method                                                                                                                                                                     | MCP-MOD                         |
| Parameter estimate                                                                                                                                                         | Relative Risk (RR)              |
| Point estimate                                                                                                                                                             | 0.99                            |
| Confidence interval                                                                                                                                                        |                                 |
| level                                                                                                                                                                      | 95 %                            |
| sides                                                                                                                                                                      | 2-sided                         |
| lower limit                                                                                                                                                                | 0.87                            |
| upper limit                                                                                                                                                                | 1.1                             |

| <b>Statistical analysis title</b>                                                                                                                                          | Milvexian 25 mg BID over Placebo |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| Statistical analysis description:<br>Multiple Comparison Procedures, MODel (MCP-MOD). 95% confidence interval (CI) for composite event based on bootstrap (10000 samples). |                                  |
| Comparison groups                                                                                                                                                          | Placebo v Milvexian 25 mg BID    |
| Number of subjects included in analysis                                                                                                                                    | 912                              |
| Analysis specification                                                                                                                                                     | Pre-specified                    |
| Analysis type                                                                                                                                                              | superiority                      |
| Method                                                                                                                                                                     | MCP-MOD                          |
| Parameter estimate                                                                                                                                                         | Relative Risk (RR)               |
| Point estimate                                                                                                                                                             | 0.99                             |
| Confidence interval                                                                                                                                                        |                                  |
| level                                                                                                                                                                      | 95 %                             |
| sides                                                                                                                                                                      | 2-sided                          |
| lower limit                                                                                                                                                                | 0.83                             |
| upper limit                                                                                                                                                                | 1.15                             |

|                                                                                                                                                                            |                                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                          | Milvexian 200 mg BID over Placebo |
| Statistical analysis description:<br>Multiple Comparison Procedures, MODel (MCP-MOD). 95% confidence interval (CI) for composite event based on bootstrap (10000 samples). |                                   |
| Comparison groups                                                                                                                                                          | Placebo v Milvexian 200 mg BID    |
| Number of subjects included in analysis                                                                                                                                    | 942                               |
| Analysis specification                                                                                                                                                     | Pre-specified                     |
| Analysis type                                                                                                                                                              | superiority                       |
| Method                                                                                                                                                                     | MCP-MOD                           |
| Parameter estimate                                                                                                                                                         | Relative Risk (RR)                |
| Point estimate                                                                                                                                                             | 0.91                              |
| Confidence interval                                                                                                                                                        |                                   |
| level                                                                                                                                                                      | 95 %                              |
| sides                                                                                                                                                                      | 2-sided                           |
| lower limit                                                                                                                                                                | 0.69                              |
| upper limit                                                                                                                                                                | 1.31                              |

|                                                                                                                                                                            |                                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                          | Milvexian 100 mg BID over Placebo |
| Statistical analysis description:<br>Multiple Comparison Procedures, MODel (MCP-MOD). 95% confidence interval (CI) for composite event based on bootstrap (10000 samples). |                                   |
| Comparison groups                                                                                                                                                          | Placebo v Milvexian 100 mg BID    |
| Number of subjects included in analysis                                                                                                                                    | 902                               |
| Analysis specification                                                                                                                                                     | Pre-specified                     |
| Analysis type                                                                                                                                                              | superiority                       |
| Method                                                                                                                                                                     | MCP-MOD                           |
| Parameter estimate                                                                                                                                                         | Relative Risk (RR)                |
| Point estimate                                                                                                                                                             | 0.92                              |
| Confidence interval                                                                                                                                                        |                                   |
| level                                                                                                                                                                      | 95 %                              |
| sides                                                                                                                                                                      | 2-sided                           |
| lower limit                                                                                                                                                                | 0.73                              |
| upper limit                                                                                                                                                                | 1.18                              |

|                                                                                                                                                                            |                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                          | Milvexian 50 mg BID over Placebo |
| Statistical analysis description:<br>Multiple Comparison Procedures, MODel (MCP-MOD). 95% confidence interval (CI) for composite event based on bootstrap (10000 samples). |                                  |
| Comparison groups                                                                                                                                                          | Placebo v Milvexian 50 mg BID    |



|                                         |                    |
|-----------------------------------------|--------------------|
| Number of subjects included in analysis | 931                |
| Analysis specification                  | Pre-specified      |
| Analysis type                           | superiority        |
| Method                                  | MCP-MOD            |
| Parameter estimate                      | Relative Risk (RR) |
| Point estimate                          | 0.93               |
| Confidence interval                     |                    |
| level                                   | 95 %               |
| sides                                   | 2-sided            |
| lower limit                             | 0.76               |
| upper limit                             | 1.16               |

## Secondary: Percent of Participants with Major Bleeding According to BARC Type 3 and 5

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                            |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Percent of Participants with Major Bleeding According to BARC Type 3 and 5 |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                            |
| Percent of participants with major bleeding based on the Bleeding Academic Research Consortium (BARC) Types 3 and 5 definitions. BARC bleeding types:<br>3a = Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL transfusion with overt bleeding<br>3b = Overt bleeding plus hemoglobin drop ≥5 g/dL; cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring IV vasoactive agents<br>3c = Intracranial hemorrhage,<br>5a = Probable fatal bleeding<br>5b = Definite fatal bleeding |                                                                            |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Secondary                                                                  |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                            |
| From first dose to up to 107 days after first dose                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                            |

| End point values                  | Placebo          | Milvexian 25 mg QD | Milvexian 25 mg BID | Milvexian 50 mg BID |
|-----------------------------------|------------------|--------------------|---------------------|---------------------|
| Subject group type                | Reporting group  | Reporting group    | Reporting group     | Reporting group     |
| Number of subjects analysed       | 682              | 325                | 313                 | 325                 |
| Units: Percentage of participants |                  |                    |                     |                     |
| number (confidence interval 95%)  | 0.6 (0.2 to 1.5) | 0.6 (0.1 to 2.2)   | 0.6 (0.1 to 2.3)    | 1.5 (0.5 to 3.6)    |

| End point values                  | Milvexian 100 mg BID | Milvexian 200 mg BID | Milvexian 50 mg QD | Milvexian 100 mg QD |
|-----------------------------------|----------------------|----------------------|--------------------|---------------------|
| Subject group type                | Reporting group      | Reporting group      | Reporting group    | Reporting group     |
| Number of subjects analysed       | 306                  | 344                  | 22                 | 17                  |
| Units: Percentage of participants |                      |                      |                    |                     |
| number (confidence interval 95%)  | 1.6 (0.5 to 3.8)     | 1.5 (0.5 to 3.4)     | 0 (0 to 15.4)      | 0 (0 to 19.5)       |

## Statistical analyses

**Secondary: Percent of Participants with Bleeding Based on BARC Types 1-5**

|                 |                                                               |
|-----------------|---------------------------------------------------------------|
| End point title | Percent of Participants with Bleeding Based on BARC Types 1-5 |
|-----------------|---------------------------------------------------------------|

End point description:

Percent of participants with bleeding based on Bleeding Academic Research Consortium (BARC) Type 1 to 5. BARC bleeding types: 0=No bleeding. 1=Not actionable bleeding. 2=Overt, actionable sign of hemorrhage requiring nonsurgical, medical intervention by a health-care professional, leading to hospitalization or increased level of care, or prompting evaluation. 3a=Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL. 3b=Overt bleeding plus hemoglobin drop  $\geq$ 5 g/dL; cardiac tamponade; bleeding requiring surgical intervention; bleeding requiring IV vasoactive agents. 3c=Intracranial hemorrhage; intraocular bleed compromising vision. 4=CABG-related bleeding, perioperative intracranial bleeding within 48 hours, reoperation after closure of sternotomy to control bleeding, transfusion of  $\geq$ 5 U whole blood or packed red blood cells within a 48-hour period, chest tube output more than or equal to 2L within a 24-hour period. 5a=Probable fatal bleeding. 5b=Definite fatal bleeding.

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

End point timeframe:

From first dose to up to 107 days after first dose

| End point values            | Placebo         | Milvexian 25 mg QD | Milvexian 25 mg BID | Milvexian 50 mg BID |
|-----------------------------|-----------------|--------------------|---------------------|---------------------|
| Subject group type          | Reporting group | Reporting group    | Reporting group     | Reporting group     |
| Number of subjects analysed | 682             | 325                | 313                 | 325                 |
| Units: Participants         |                 |                    |                     |                     |
| TYPE 1                      | 41              | 26                 | 16                  | 28                  |
| TYPE 2                      | 9               | 7                  | 9                   | 7                   |
| TYPE 3A                     | 2               | 1                  | 1                   | 1                   |
| TYPE 3B                     | 0               | 1                  | 1                   | 1                   |
| TYPE 3C                     | 2               | 0                  | 0                   | 3                   |
| TYPE 4                      | 0               | 0                  | 0                   | 0                   |
| TYPE 5A                     | 0               | 0                  | 0                   | 0                   |
| TYPE 5B                     | 0               | 0                  | 0                   | 0                   |

| End point values            | Milvexian 100 mg BID | Milvexian 200 mg BID | Milvexian 50 mg QD | Milvexian 100 mg QD |
|-----------------------------|----------------------|----------------------|--------------------|---------------------|
| Subject group type          | Reporting group      | Reporting group      | Reporting group    | Reporting group     |
| Number of subjects analysed | 306                  | 344                  | 22                 | 17                  |
| Units: Participants         |                      |                      |                    |                     |
| TYPE 1                      | 25                   | 22                   | 5                  | 2                   |
| TYPE 2                      | 10                   | 8                    | 1                  | 1                   |
| TYPE 3A                     | 2                    | 3                    | 0                  | 0                   |
| TYPE 3B                     | 3                    | 1                    | 0                  | 0                   |
| TYPE 3C                     | 0                    | 1                    | 0                  | 0                   |
| TYPE 4                      | 0                    | 0                    | 0                  | 0                   |
| TYPE 5A                     | 0                    | 0                    | 0                  | 0                   |
| TYPE 5B                     | 0                    | 0                    | 0                  | 0                   |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Bleeding Based on ISTH-Defined Criteria

|                 |                                                                     |
|-----------------|---------------------------------------------------------------------|
| End point title | Number of Participants with Bleeding Based on ISTH-Defined Criteria |
|-----------------|---------------------------------------------------------------------|

End point description:

Number of participants with bleeding based on International Society on Thrombosis and Hemostasis (ISTH). ISTH Bleeding Types: 1) Fatal bleeding and/or 2) Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome and/or 3) Bleeding causing a fall in hemoglobin level of  $\geq 2$  g/dL, or leading to transfusion of  $\geq 2$  units of whole blood or red cells.

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

End point timeframe:

From first dose to up to 107 days after first dose

| End point values            | Placebo         | Milvexian 25 mg QD | Milvexian 25 mg BID | Milvexian 50 mg BID |
|-----------------------------|-----------------|--------------------|---------------------|---------------------|
| Subject group type          | Reporting group | Reporting group    | Reporting group     | Reporting group     |
| Number of subjects analysed | 682             | 325                | 313                 | 325                 |
| Units: Participants         |                 |                    |                     |                     |
| MAJOR                       | 4               | 2                  | 2                   | 5                   |
| CRNM                        | 7               | 8                  | 9                   | 7                   |
| MAJOR OR CRNM               | 11              | 10                 | 11                  | 12                  |
| MINOR BLEED                 | 43              | 25                 | 16                  | 28                  |

| End point values            | Milvexian 100 mg BID | Milvexian 200 mg BID | Milvexian 50 mg QD | Milvexian 100 mg QD |
|-----------------------------|----------------------|----------------------|--------------------|---------------------|
| Subject group type          | Reporting group      | Reporting group      | Reporting group    | Reporting group     |
| Number of subjects analysed | 306                  | 344                  | 22                 | 17                  |
| Units: Participants         |                      |                      |                    |                     |
| MAJOR                       | 6                    | 5                    | 0                  | 0                   |
| CRNM                        | 8                    | 8                    | 1                  | 1                   |
| MAJOR OR CRNM               | 14                   | 13                   | 1                  | 1                   |
| MINOR BLEED                 | 26                   | 22                   | 5                  | 2                   |

## Statistical analyses

**Secondary: Number of Participants with Bleeding Based on PLATO-Defined Criteria**

|                 |                                                                      |
|-----------------|----------------------------------------------------------------------|
| End point title | Number of Participants with Bleeding Based on PLATO-Defined Criteria |
|-----------------|----------------------------------------------------------------------|

End point description:

Number of participants with bleeding based on Platelet Inhibition and Patient Outcomes (PLATO) defined criteria. PLATO bleeding definitions:

1. Major Life-threatening: Fatal, Intracranial, Intrapericardial with cardiac tamponade, Resulting in hypovolemic shock or severe hypotension that requires pressors or surgery, Clinically overt or apparent bleeding associated with decrease in hemoglobin >5 g/dL, Requiring transfusion of  $\geq 4$  U whole blood or packed red blood cells (PRBCs)
2. Other Major: Significantly disabling (eg, intraocular with permanent vision loss), Associated drop in hemoglobin of 3 to 5 g/dL, Requiring transfusion of 2 to 3 U whole blood or PRBCs
3. Any Major: Any one of the above criteria
4. Minor: Bleeding that does not meet criteria for PLATO Major bleeding, and requiring medical intervention

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

End point timeframe:

From first dose to up to 107 days after first dose

| End point values            | Placebo         | Milvexian 25 mg QD | Milvexian 25 mg BID | Milvexian 50 mg BID |
|-----------------------------|-----------------|--------------------|---------------------|---------------------|
| Subject group type          | Reporting group | Reporting group    | Reporting group     | Reporting group     |
| Number of subjects analysed | 682             | 325                | 313                 | 325                 |
| Units: Participants         |                 |                    |                     |                     |
| MAJOR LIFE-THREATENING      | 2               | 1                  | 1                   | 4                   |
| OTHER MAJOR BLEEDING        | 2               | 1                  | 1                   | 1                   |
| ANY MAJOR                   | 4               | 2                  | 2                   | 5                   |
| MINOR                       | 7               | 6                  | 7                   | 7                   |
| MINIMAL                     | 43              | 27                 | 18                  | 28                  |

| End point values            | Milvexian 100 mg BID | Milvexian 200 mg BID | Milvexian 50 mg QD | Milvexian 100 mg QD |
|-----------------------------|----------------------|----------------------|--------------------|---------------------|
| Subject group type          | Reporting group      | Reporting group      | Reporting group    | Reporting group     |
| Number of subjects analysed | 306                  | 344                  | 22                 | 17                  |
| Units: Participants         |                      |                      |                    |                     |
| MAJOR LIFE-THREATENING      | 3                    | 2                    | 0                  | 0                   |
| OTHER MAJOR BLEEDING        | 2                    | 3                    | 0                  | 0                   |
| ANY MAJOR                   | 5                    | 5                    | 0                  | 0                   |
| MINOR                       | 9                    | 9                    | 0                  | 1                   |
| MINIMAL                     | 26                   | 21                   | 6                  | 2                   |

**Statistical analyses**

No statistical analyses for this end point

## Secondary: Percent of Participants with Descriptive Assessment of Composite of New Ischemic Stroke During Treatment and New Covert Brain Infarction (FLAIR + DWI) Detected by MRI by Day 90

|                 |                                                                                                                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percent of Participants with Descriptive Assessment of Composite of New Ischemic Stroke During Treatment and New Covert Brain Infarction (FLAIR + DWI) Detected by MRI by Day 90 <sup>[2]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Descriptive Assessment of Composite of New Ischemic Stroke During Treatment and New Covert Brain Infarction (FLAIR + DWI) Detected by MRI by Day 90.

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

End point timeframe:

From randomization to up to 90 days after randomization

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Endpoints are cohort specific and do not report for all arms.

| End point values                  | Placebo         | Milvexian 25 mg QD | Milvexian 25 mg BID | Milvexian 50 mg BID |
|-----------------------------------|-----------------|--------------------|---------------------|---------------------|
| Subject group type                | Reporting group | Reporting group    | Reporting group     | Reporting group     |
| Number of subjects analysed       | 625             | 308                | 287                 | 306                 |
| Units: Percentage of participants |                 |                    |                     |                     |
| number (not applicable)           | 16.6            | 16.2               | 18.5                | 14.1                |

| End point values                  | Milvexian 100 mg BID | Milvexian 200 mg BID |  |  |
|-----------------------------------|----------------------|----------------------|--|--|
| Subject group type                | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed       | 277                  | 317                  |  |  |
| Units: Percentage of participants |                      |                      |  |  |
| number (not applicable)           | 14.8                 | 16.4                 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Composite of Percent of Participants with New Ischemic Stroke, MI and All Cause Death

|                 |                                                                                       |
|-----------------|---------------------------------------------------------------------------------------|
| End point title | Composite of Percent of Participants with New Ischemic Stroke, MI and All Cause Death |
|-----------------|---------------------------------------------------------------------------------------|

End point description:

Composite of percent of participants of new ischemic stroke, (Myocardial Infarction) MI and all cause death.

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

End point timeframe:

From randomization to up to 90 days after randomization

| End point values                  | Placebo          | Milvexian 25 mg QD | Milvexian 25 mg BID | Milvexian 50 mg BID |
|-----------------------------------|------------------|--------------------|---------------------|---------------------|
| Subject group type                | Reporting group  | Reporting group    | Reporting group     | Reporting group     |
| Number of subjects analysed       | 691              | 328                | 318                 | 328                 |
| Units: Percentage of participants |                  |                    |                     |                     |
| number (confidence interval 95%)  | 6.1 (4.3 to 7.9) | 5.2 (2.8 to 7.6)   | 4.7 (2.4 to 7.0)    | 4.9 (2.5 to 7.2)    |

| End point values                  | Milvexian 100 mg BID | Milvexian 200 mg BID | Milvexian 50 mg QD | Milvexian 100 mg QD |
|-----------------------------------|----------------------|----------------------|--------------------|---------------------|
| Subject group type                | Reporting group      | Reporting group      | Reporting group    | Reporting group     |
| Number of subjects analysed       | 310                  | 351                  | 22                 | 18                  |
| Units: Percentage of participants |                      |                      |                    |                     |
| number (confidence interval 95%)  | 5.2 (2.7 to 7.6)     | 9.4 (6.3 to 12.5)    | 18.2 (2.1 to 34.3) | 5.6 (0 to 16.1)     |

## Statistical analyses

No statistical analyses for this end point

## Secondary: National Institutes of Health Stroke Scale (NIHSS)

|                 |                                                    |
|-----------------|----------------------------------------------------|
| End point title | National Institutes of Health Stroke Scale (NIHSS) |
|-----------------|----------------------------------------------------|

End point description:

The NIHSS is an 11-item neurologic examination stroke scale used to evaluate the effect of acute cerebral infarction on the levels of consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss. A trained observer rates the patient's ability to answer questions and perform activities. The score for each ability is a number between 0 and 4, 0 being normal functioning and 4 being completely impaired. The patient's NIHSS score is calculated by adding the number for each element of the scale; 42 is the highest score possible. In the NIHSS, the higher the score, the more impaired a stroke participant is. 99999 = Not Available

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

End point timeframe:

At baseline, on Days 21 and 90, and at the time of a new stroke event

| End point values                     | Placebo         | Milvexian 25 mg QD | Milvexian 25 mg BID | Milvexian 50 mg BID |
|--------------------------------------|-----------------|--------------------|---------------------|---------------------|
| Subject group type                   | Reporting group | Reporting group    | Reporting group     | Reporting group     |
| Number of subjects analysed          | 684             | 324                | 311                 | 326                 |
| Units: Score on a scale              |                 |                    |                     |                     |
| arithmetic mean (standard deviation) |                 |                    |                     |                     |
| Baseline                             | 1.6 (± 1.87)    | 1.7 (± 1.68)       | 1.6 (± 1.73)        | 1.6 (± 1.79)        |
| Day 21                               | 0.9 (± 2.11)    | 0.8 (± 1.35)       | 0.8 (± 1.43)        | 0.8 (± 1.58)        |
| Day 90                               | 0.5 (± 1.40)    | 0.6 (± 1.06)       | 0.6 (± 1.51)        | 0.6 (± 1.14)        |
| First recurrent stroke               | 6.2 (± 5.01)    | 4.6 (± 6.79)       | 5.4 (± 3.17)        | 4.6 (± 4.30)        |

| End point values                     | Milvexian 100 mg BID | Milvexian 200 mg BID | Milvexian 50 mg QD | Milvexian 100 mg QD |
|--------------------------------------|----------------------|----------------------|--------------------|---------------------|
| Subject group type                   | Reporting group      | Reporting group      | Reporting group    | Reporting group     |
| Number of subjects analysed          | 305                  | 348                  | 22                 | 17                  |
| Units: Score on a scale              |                      |                      |                    |                     |
| arithmetic mean (standard deviation) |                      |                      |                    |                     |
| Baseline                             | 1.8 (± 1.81)         | 1.6 (± 1.79)         | 1.1 (± 1.44)       | 2.0 (± 1.70)        |
| Day 21                               | 0.8 (± 1.48)         | 0.9 (± 1.88)         | 0.8 (± 1.90)       | 0.9 (± 1.39)        |
| Day 90                               | 0.6 (± 1.32)         | 0.6 (± 1.29)         | 0.3 (± 0.72)       | 0.6 (± 1.45)        |
| First recurrent stroke               | 7.1 (± 4.68)         | 4.4 (± 4.60)         | 5.3 (± 3.06)       | 1.0 (± 99999)       |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Modified Rankin Scale (mRS)

|                                                                                                                           |                             |
|---------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| End point title                                                                                                           | Modified Rankin Scale (mRS) |
| End point description:                                                                                                    |                             |
| The Modified Rankin Score (mRS) is a 6-point disability scale with possible scores ranging from 0 to 6.                   |                             |
| 0 = No symptoms at all                                                                                                    |                             |
| 1 = No significant disability despite symptoms; able to carry out all usual duties and activities                         |                             |
| 2 = Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance |                             |
| 3 = Moderate disability; requiring some help, but able to walk without assistance                                         |                             |
| 4 = Moderately severe disability; unable to walk and attend to bodily needs without assistance                            |                             |
| 5 = Severe disability; bedridden, incontinent and requiring constant nursing care and attention                           |                             |
| 6 = Dead                                                                                                                  |                             |
| 99999 = Not Available                                                                                                     |                             |
| End point type                                                                                                            | Secondary                   |
| End point timeframe:                                                                                                      |                             |
| At baseline, on Days 21 and 90, and at the time of a new stroke event                                                     |                             |

| End point values                     | Placebo         | Milvexian 25 mg QD | Milvexian 25 mg BID | Milvexian 50 mg BID |
|--------------------------------------|-----------------|--------------------|---------------------|---------------------|
| Subject group type                   | Reporting group | Reporting group    | Reporting group     | Reporting group     |
| Number of subjects analysed          | 688             | 326                | 314                 | 328                 |
| Units: Score on a scale              |                 |                    |                     |                     |
| arithmetic mean (standard deviation) |                 |                    |                     |                     |
| Baseline                             | 0.5 (± 0.87)    | 0.6 (± 0.95)       | 0.6 (± 0.96)        | 0.5 (± 0.86)        |
| Day 21                               | 1.0 (± 1.18)    | 1.0 (± 1.13)       | 0.9 (± 1.15)        | 0.9 (± 1.15)        |
| Day 90                               | 0.7 (± 1.04)    | 0.8 (± 1.04)       | 0.8 (± 1.07)        | 0.7 (± 1.01)        |
| First recurrent stroke               | 3.0 (± 1.60)    | 2.7 (± 1.03)       | 2.6 (± 1.35)        | 2.3 (± 1.62)        |

| End point values            | Milvexian 100 mg BID | Milvexian 200 mg BID | Milvexian 50 mg QD | Milvexian 100 mg QD |
|-----------------------------|----------------------|----------------------|--------------------|---------------------|
| Subject group type          | Reporting group      | Reporting group      | Reporting group    | Reporting group     |
| Number of subjects analysed | 309                  | 349                  | 22                 | 17                  |

|                                      |              |              |              |               |
|--------------------------------------|--------------|--------------|--------------|---------------|
| Units: Score on a scale              |              |              |              |               |
| arithmetic mean (standard deviation) |              |              |              |               |
| Baseline                             | 0.5 (± 0.89) | 0.6 (± 0.95) | 0.2 (± 0.53) | 0.7 (± 0.99)  |
| Day 21                               | 1.0 (± 1.17) | 0.9 (± 1.19) | 0.9 (± 1.27) | 1.3 (± 1.14)  |
| Day 90                               | 0.7 (± 1.01) | 0.8 (± 1.05) | 0.6 (± 1.05) | 1.0 (± 1.11)  |
| First recurrent stroke               | 2.9 (± 1.64) | 1.8 (± 1.72) | 2.0 (± 0.00) | 1.0 (± 99999) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Montreal Cognitive Assessment (MoCA)

|                                                                                                                                                                                             |                                      |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| End point title                                                                                                                                                                             | Montreal Cognitive Assessment (MoCA) |
| End point description:                                                                                                                                                                      |                                      |
| The Montreal Cognitive Assessment (MoCA) is a survey with a score summed, with a highest total score of 30. A score of $\geq 26$ indicates normal cognitive function. 99999 = Not Available |                                      |
| End point type                                                                                                                                                                              | Secondary                            |
| End point timeframe:                                                                                                                                                                        |                                      |
| At baseline, on Days 21 and 90, and at the time of a new stroke event                                                                                                                       |                                      |

| End point values                     | Placebo         | Milvexian 25 mg QD | Milvexian 25 mg BID | Milvexian 50 mg BID |
|--------------------------------------|-----------------|--------------------|---------------------|---------------------|
| Subject group type                   | Reporting group | Reporting group    | Reporting group     | Reporting group     |
| Number of subjects analysed          | 541             | 257                | 235                 | 257                 |
| Units: Score on a scale              |                 |                    |                     |                     |
| arithmetic mean (standard deviation) |                 |                    |                     |                     |
| Baseline                             | 22.3 (± 5.06)   | 21.6 (± 5.59)      | 22.0 (± 5.18)       | 22.5 (± 4.82)       |
| Day 21                               | 24.0 (± 4.77)   | 23.9 (± 5.01)      | 24.0 (± 4.70)       | 24.3 (± 4.57)       |
| Day 90                               | 24.6 (± 4.54)   | 24.0 (± 4.69)      | 24.2 (± 4.80)       | 24.4 (± 4.48)       |
| First recurrent stroke               | 23.2 (± 6.63)   | 17.3 (± 6.11)      | 25.3 (± 2.31)       | 19.0 (± 8.49)       |

| End point values                     | Milvexian 100 mg BID | Milvexian 200 mg BID | Milvexian 50 mg QD | Milvexian 100 mg QD |
|--------------------------------------|----------------------|----------------------|--------------------|---------------------|
| Subject group type                   | Reporting group      | Reporting group      | Reporting group    | Reporting group     |
| Number of subjects analysed          | 235                  | 276                  | 17                 | 14                  |
| Units: Score on a scale              |                      |                      |                    |                     |
| arithmetic mean (standard deviation) |                      |                      |                    |                     |
| Baseline                             | 22.4 (± 5.04)        | 22.1 (± 5.31)        | 24.4 (± 3.84)      | 22.0 (± 4.59)       |
| Day 21                               | 23.6 (± 4.48)        | 24.0 (± 4.96)        | 26.4 (± 2.61)      | 24.1 (± 4.70)       |
| Day 90                               | 24.5 (± 4.36)        | 24.2 (± 5.05)        | 25.0 (± 4.72)      | 26.4 (± 1.69)       |
| First recurrent stroke               | 3.0 (± 99999)        | 23.1 (± 7.08)        | 11.0 (± 99999)     | 22.0 (± 99999)      |



## Statistical analyses

No statistical analyses for this end point

### Secondary: Digit Symbol Substitution Test (DSST)

|                 |                                       |
|-----------------|---------------------------------------|
| End point title | Digit Symbol Substitution Test (DSST) |
|-----------------|---------------------------------------|

End point description:

The Descriptive Summary of the Digit Symbol Substitution Test (DSST) is a scale item, with a highest total score of 135. Higher score indicates better cognitive functioning. 99999 = Not Available

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

End point timeframe:

At baseline, on Days 21 and 90, and at the time of a new stroke event

| End point values                     | Placebo         | Milvexian 25 mg QD | Milvexian 25 mg BID | Milvexian 50 mg BID |
|--------------------------------------|-----------------|--------------------|---------------------|---------------------|
| Subject group type                   | Reporting group | Reporting group    | Reporting group     | Reporting group     |
| Number of subjects analysed          | 493             | 238                | 209                 | 234                 |
| Units: Score on a scale              |                 |                    |                     |                     |
| arithmetic mean (standard deviation) |                 |                    |                     |                     |
| Baseline                             | 34.9 (± 22.36)  | 31.2 (± 18.87)     | 32.9 (± 22.89)      | 37.2 (± 25.67)      |
| Day 21                               | 41.2 (± 22.14)  | 38.9 (± 19.27)     | 40.2 (± 21.60)      | 45.1 (± 25.77)      |
| Day 90                               | 42.8 (± 21.18)  | 41.7 (± 21.66)     | 41.3 (± 20.29)      | 45.2 (± 21.86)      |
| First recurrent stroke               | 36.3 (± 13.56)  | 28.0 (± 20.95)     | 42.0 (± 4.36)       | 40.5 (± 2.12)       |

| End point values                     | Milvexian 100 mg BID | Milvexian 200 mg BID | Milvexian 50 mg QD | Milvexian 100 mg QD |
|--------------------------------------|----------------------|----------------------|--------------------|---------------------|
| Subject group type                   | Reporting group      | Reporting group      | Reporting group    | Reporting group     |
| Number of subjects analysed          | 220                  | 257                  | 17                 | 14                  |
| Units: Score on a scale              |                      |                      |                    |                     |
| arithmetic mean (standard deviation) |                      |                      |                    |                     |
| Baseline                             | 33.7 (± 21.89)       | 31.7 (± 19.15)       | 47.1 (± 29.34)     | 29.2 (± 18.16)      |
| Day 21                               | 41.2 (± 22.87)       | 39.1 (± 21.35)       | 54.6 (± 32.73)     | 37.1 (± 20.13)      |
| Day 90                               | 45.5 (± 23.44)       | 41.4 (± 21.97)       | 47.5 (± 27.48)     | 40.7 (± 17.46)      |
| First recurrent stroke               | 23.0 (± 99999)       | 27.5 (± 16.96)       | 9.0 (± 99999)      | 47.0 (± 99999)      |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Adverse Events (AEs)

|                 |                                                  |
|-----------------|--------------------------------------------------|
| End point title | Number of Participants with Adverse Events (AEs) |
|-----------------|--------------------------------------------------|

End point description:

AE: include all non-serious adverse events with onset on or after first dose date and within 2 days after the last dose of study treatment.

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

End point timeframe:

From first dose to 2 days after last dose of study therapy (up to approximately 107 days)

| End point values            | Placebo         | Milvexian 25 mg QD | Milvexian 25 mg BID | Milvexian 50 mg BID |
|-----------------------------|-----------------|--------------------|---------------------|---------------------|
| Subject group type          | Reporting group | Reporting group    | Reporting group     | Reporting group     |
| Number of subjects analysed | 682             | 325                | 313                 | 325                 |
| Units: Participants         | 399             | 190                | 186                 | 192                 |

| End point values            | Milvexian 100 mg BID | Milvexian 200 mg BID | Milvexian 50 mg QD | Milvexian 100 mg QD |
|-----------------------------|----------------------|----------------------|--------------------|---------------------|
| Subject group type          | Reporting group      | Reporting group      | Reporting group    | Reporting group     |
| Number of subjects analysed | 306                  | 344                  | 22                 | 17                  |
| Units: Participants         | 193                  | 211                  | 11                 | 13                  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Clinically Significant Vital Sign Abnormalities

|                 |                                                                             |
|-----------------|-----------------------------------------------------------------------------|
| End point title | Number of Participants with Clinically Significant Vital Sign Abnormalities |
|-----------------|-----------------------------------------------------------------------------|

End point description:

Number of participants with clinically significant vital sign abnormalities. Vital signs included heart rate and diastolic and systolic blood pressure.

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

End point timeframe:

At day 21 and day 90

| End point values            | Placebo         | Milvexian 25 mg QD | Milvexian 25 mg BID | Milvexian 50 mg BID |
|-----------------------------|-----------------|--------------------|---------------------|---------------------|
| Subject group type          | Reporting group | Reporting group    | Reporting group     | Reporting group     |
| Number of subjects analysed | 682             | 325                | 313                 | 325                 |
| Units: Participants         | 0               | 0                  | 0                   | 0                   |

| End point values            | Milvexian 100 mg BID | Milvexian 200 mg BID | Milvexian 50 mg QD | Milvexian 100 mg QD |
|-----------------------------|----------------------|----------------------|--------------------|---------------------|
| Subject group type          | Reporting group      | Reporting group      | Reporting group    | Reporting group     |
| Number of subjects analysed | 306                  | 344                  | 22                 | 17                  |

|                     |   |   |   |   |
|---------------------|---|---|---|---|
| Units: Participants | 0 | 0 | 0 | 0 |
|---------------------|---|---|---|---|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Clinically Significant Physical Examination Abnormalities

|                        |                                                                                        |
|------------------------|----------------------------------------------------------------------------------------|
| End point title        | Number of Participants with Clinically Significant Physical Examination Abnormalities  |
| End point description: | Number of participants with clinically significant physical examination abnormalities. |
| End point type         | Secondary                                                                              |
| End point timeframe:   | At day 21 and day 90                                                                   |

| End point values            | Placebo         | Milvexian 25 mg QD | Milvexian 25 mg BID | Milvexian 50 mg BID |
|-----------------------------|-----------------|--------------------|---------------------|---------------------|
| Subject group type          | Reporting group | Reporting group    | Reporting group     | Reporting group     |
| Number of subjects analysed | 682             | 325                | 313                 | 325                 |
| Units: Participants         | 0               | 0                  | 0                   | 0                   |

| End point values            | Milvexian 100 mg BID | Milvexian 200 mg BID | Milvexian 50 mg QD | Milvexian 100 mg QD |
|-----------------------------|----------------------|----------------------|--------------------|---------------------|
| Subject group type          | Reporting group      | Reporting group      | Reporting group    | Reporting group     |
| Number of subjects analysed | 306                  | 344                  | 22                 | 17                  |
| Units: Participants         | 0                    | 0                    | 0                  | 0                   |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Clinically Significant Electrocardiogram (ECG) Abnormalities

|                        |                                                                                          |
|------------------------|------------------------------------------------------------------------------------------|
| End point title        | Number of Participants with Clinically Significant Electrocardiogram (ECG) Abnormalities |
| End point description: | Number of participants with clinically significant ECG abnormalities.                    |
| End point type         | Secondary                                                                                |
| End point timeframe:   | At day 21 and day 90                                                                     |

| End point values            | Placebo         | Milvexian 25 mg QD | Milvexian 25 mg BID | Milvexian 50 mg BID |
|-----------------------------|-----------------|--------------------|---------------------|---------------------|
| Subject group type          | Reporting group | Reporting group    | Reporting group     | Reporting group     |
| Number of subjects analysed | 682             | 325                | 313                 | 325                 |
| Units: Participants         | 0               | 0                  | 0                   | 0                   |

| End point values            | Milvexian 100 mg BID | Milvexian 200 mg BID | Milvexian 50 mg QD | Milvexian 100 mg QD |
|-----------------------------|----------------------|----------------------|--------------------|---------------------|
| Subject group type          | Reporting group      | Reporting group      | Reporting group    | Reporting group     |
| Number of subjects analysed | 306                  | 344                  | 22                 | 17                  |
| Units: Participants         | 0                    | 0                    | 0                  | 0                   |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Clinically Significant Laboratory Abnormalities - Liver

|                 |                                                                                     |
|-----------------|-------------------------------------------------------------------------------------|
| End point title | Number of Participants with Clinically Significant Laboratory Abnormalities - Liver |
|-----------------|-------------------------------------------------------------------------------------|

End point description:

The number of treated participants who experienced a laboratory abnormality of the liver during the course of the study.

Aspartate aminotransferase (AST)

Alanine aminotransferase (ALT)

Upper Limit of Normal (ULN)

Results reported in International System of Units (SI)

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

End point timeframe:

From first dose to up to approximately 38 months

| End point values            | Placebo         | Milvexian 25 mg QD | Milvexian 25 mg BID | Milvexian 50 mg BID |
|-----------------------------|-----------------|--------------------|---------------------|---------------------|
| Subject group type          | Reporting group | Reporting group    | Reporting group     | Reporting group     |
| Number of subjects analysed | 642             | 303                | 280                 | 306                 |
| Units: Participants         |                 |                    |                     |                     |
| ALT > 3x ULN                | 4               | 2                  | 0                   | 2                   |
| ALT > 5x ULN                | 1               | 0                  | 0                   | 0                   |
| ALT > 10x ULN               | 1               | 0                  | 0                   | 0                   |
| ALT > 20x ULN               | 0               | 0                  | 0                   | 0                   |
| AST > 3x ULN                | 6               | 5                  | 1                   | 4                   |
| AST > 5x ULN                | 3               | 2                  | 1                   | 0                   |

|                                               |    |   |   |   |
|-----------------------------------------------|----|---|---|---|
| AST > 10x ULN                                 | 1  | 0 | 0 | 0 |
| AST > 20x ULN                                 | 0  | 0 | 0 | 0 |
| ALP > 2x ULN                                  | 4  | 5 | 1 | 6 |
| Total Bilirubin > 1.5x ULN                    | 10 | 6 | 2 | 7 |
| Total Bilirubin > 2x ULN                      | 3  | 1 | 1 | 2 |
| ALT/AST elevation >3xULN w/ total bili >2xULN | 0  | 0 | 0 | 0 |

| End point values                              | Milvexian 100 mg BID | Milvexian 200 mg BID | Milvexian 50 mg QD | Milvexian 100 mg QD |
|-----------------------------------------------|----------------------|----------------------|--------------------|---------------------|
| Subject group type                            | Reporting group      | Reporting group      | Reporting group    | Reporting group     |
| Number of subjects analysed                   | 281                  | 324                  | 21                 | 16                  |
| Units: Participants                           |                      |                      |                    |                     |
| ALT > 3x ULN                                  | 3                    | 3                    | 0                  | 0                   |
| ALT > 5x ULN                                  | 2                    | 2                    | 0                  | 0                   |
| ALT > 10x ULN                                 | 1                    | 1                    | 0                  | 0                   |
| ALT > 20x ULN                                 | 1                    | 0                    | 0                  | 0                   |
| AST > 3x ULN                                  | 3                    | 3                    | 1                  | 0                   |
| AST > 5x ULN                                  | 2                    | 1                    | 1                  | 0                   |
| AST > 10x ULN                                 | 1                    | 0                    | 0                  | 0                   |
| AST > 20x ULN                                 | 1                    | 0                    | 0                  | 0                   |
| ALP > 2x ULN                                  | 4                    | 2                    | 0                  | 0                   |
| Total Bilirubin > 1.5x ULN                    | 5                    | 2                    | 0                  | 0                   |
| Total Bilirubin > 2x ULN                      | 2                    | 1                    | 0                  | 0                   |
| ALT/AST elevation >3xULN w/ total bili >2xULN | 1                    | 0                    | 0                  | 0                   |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetic Parameter - Estimated Clearance (CL)

|                 |                                                                     |
|-----------------|---------------------------------------------------------------------|
| End point title | Pharmacokinetic Parameter - Estimated Clearance (CL) <sup>[3]</sup> |
|-----------------|---------------------------------------------------------------------|

End point description:

Pharmacokinetic Parameter - Estimated Clearance (CL). CL is derived from plasma concentration versus time data.

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

End point timeframe:

Day 1, 21, 90

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Endpoints are cohort specific and do not report for all arms.

| End point values                                    | Milvexian 25 mg QD | Milvexian 25 mg BID | Milvexian 50 mg BID | Milvexian 100 mg BID |
|-----------------------------------------------------|--------------------|---------------------|---------------------|----------------------|
| Subject group type                                  | Reporting group    | Reporting group     | Reporting group     | Reporting group      |
| Number of subjects analysed                         | 323                | 307                 | 323                 | 303                  |
| Units: L/h                                          |                    |                     |                     |                      |
| geometric mean (geometric coefficient of variation) | 8.15 (± 34)        | 8.01 (± 34.3)       | 7.54 (± 32.8)       | 7.08 (± 31.3)        |

| End point values                                    | Milvexian 200 mg BID |  |  |  |
|-----------------------------------------------------|----------------------|--|--|--|
| Subject group type                                  | Reporting group      |  |  |  |
| Number of subjects analysed                         | 341                  |  |  |  |
| Units: L/h                                          |                      |  |  |  |
| geometric mean (geometric coefficient of variation) | 7.43 (± 32.9)        |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetic Parameter - Volume of the Central Compartment (VC)

|                 |                                                                                   |
|-----------------|-----------------------------------------------------------------------------------|
| End point title | Pharmacokinetic Parameter - Volume of the Central Compartment (VC) <sup>[4]</sup> |
|-----------------|-----------------------------------------------------------------------------------|

End point description:

Pharmacokinetic Parameter - Volume of the Central Compartment (VC). VC is derived from plasma concentration versus time data.

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

End point timeframe:

Day 1, 21, 90

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Endpoints are cohort specific and do not report for all arms.

| End point values                                    | Milvexian 25 mg QD | Milvexian 25 mg BID | Milvexian 50 mg BID | Milvexian 100 mg BID |
|-----------------------------------------------------|--------------------|---------------------|---------------------|----------------------|
| Subject group type                                  | Reporting group    | Reporting group     | Reporting group     | Reporting group      |
| Number of subjects analysed                         | 323                | 307                 | 323                 | 303                  |
| Units: Liter                                        |                    |                     |                     |                      |
| geometric mean (geometric coefficient of variation) | 34.9 (± 152)       | 31.4 (± 138)        | 30.9 (± 145)        | 28.9 (± 149)         |

| End point values            | Milvexian 200 mg BID |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Reporting group      |  |  |  |
| Number of subjects analysed | 341                  |  |  |  |
| Units: Liter                |                      |  |  |  |

|                                                     |                   |  |  |  |
|-----------------------------------------------------|-------------------|--|--|--|
| geometric mean (geometric coefficient of variation) | 31.6 ( $\pm$ 181) |  |  |  |
|-----------------------------------------------------|-------------------|--|--|--|

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Percent of Participants with Ischemic Stroke Events

|                                                                                                                                                                                           |                                                     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| End point title                                                                                                                                                                           | Percent of Participants with Ischemic Stroke Events |
| End point description:<br>Secondary analysis of symptomatic ischemic stroke events. Clinical events are included up to day 90. Wald 95% CI within group. Undetermined stroke is included. |                                                     |
| End point type                                                                                                                                                                            | Other pre-specified                                 |
| End point timeframe:<br>From randomization to up to 90 days after randomization                                                                                                           |                                                     |

| End point values                  | Placebo          | Milvexian 25 mg QD | Milvexian 25 mg BID | Milvexian 50 mg BID |
|-----------------------------------|------------------|--------------------|---------------------|---------------------|
| Subject group type                | Reporting group  | Reporting group    | Reporting group     | Reporting group     |
| Number of subjects analysed       | 691              | 328                | 318                 | 328                 |
| Units: Percentage of participants |                  |                    |                     |                     |
| number (confidence interval 95%)  |                  |                    |                     |                     |
| Ischemic stroke                   | 5.5 (3.8 to 7.2) | 4.6 (2.3 to 6.8)   | 3.8 (1.7 to 5.9)    | 4.0 (1.9 to 6.1)    |
| Undetermined stroke               | 0 (0 to 0)       | 0 (0 to 0)         | 0 (0 to 0)          | 0 (0 to 0)          |

| End point values                  | Milvexian 100 mg BID | Milvexian 200 mg BID | Milvexian 50 mg QD | Milvexian 100 mg QD |
|-----------------------------------|----------------------|----------------------|--------------------|---------------------|
| Subject group type                | Reporting group      | Reporting group      | Reporting group    | Reporting group     |
| Number of subjects analysed       | 310                  | 351                  | 22                 | 18                  |
| Units: Percentage of participants |                      |                      |                    |                     |
| number (confidence interval 95%)  |                      |                      |                    |                     |
| Ischemic stroke                   | 3.5 (1.5 to 5.6)     | 7.7 (4.9 to 10.5)    | 13.6 (0.0 to 28.0) | 5.6 (0.0 to 16.1)   |
| Undetermined stroke               | 0 (0 to 0)           | 0 (0 to 0)           | 0 (0 to 0)         | 0 (0 to 0)          |

## Statistical analyses

|                                                                                                                           |                                 |
|---------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Statistical analysis title                                                                                                | Milvexian 25 mg QD over Placebo |
| Statistical analysis description:<br>Wald Confidence Limits. 95% CIs for RR are constructed using Wald Confidence Limits. |                                 |
| Comparison groups                                                                                                         | Placebo v Milvexian 25 mg QD    |

|                                         |                        |
|-----------------------------------------|------------------------|
| Number of subjects included in analysis | 1019                   |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| Method                                  | Wald Confidence Limits |
| Parameter estimate                      | Relative Risk (RR)     |
| Point estimate                          | 0.83                   |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | 0.46                   |
| upper limit                             | 1.49                   |

|                                                                                                                           |                                  |
|---------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| <b>Statistical analysis title</b>                                                                                         | Milvexian 50 mg BID over Placebo |
| Statistical analysis description:<br>Wald Confidence Limits. 95% CIs for RR are constructed using Wald Confidence Limits. |                                  |
| Comparison groups                                                                                                         | Placebo v Milvexian 50 mg BID    |
| Number of subjects included in analysis                                                                                   | 1019                             |
| Analysis specification                                                                                                    | Pre-specified                    |
| Analysis type                                                                                                             | superiority                      |
| Method                                                                                                                    | Wald Confidence Limits           |
| Parameter estimate                                                                                                        | Relative Risk (RR)               |
| Point estimate                                                                                                            | 0.72                             |
| Confidence interval                                                                                                       |                                  |
| level                                                                                                                     | 95 %                             |
| sides                                                                                                                     | 2-sided                          |
| lower limit                                                                                                               | 0.39                             |
| upper limit                                                                                                               | 1.33                             |

|                                                                                                                           |                                  |
|---------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| <b>Statistical analysis title</b>                                                                                         | Milvexian 100 mg QD over Placebo |
| Statistical analysis description:<br>Wald Confidence Limits. 95% CIs for RR are constructed using Wald Confidence Limits. |                                  |
| Comparison groups                                                                                                         | Placebo v Milvexian 100 mg QD    |
| Number of subjects included in analysis                                                                                   | 709                              |
| Analysis specification                                                                                                    | Pre-specified                    |
| Analysis type                                                                                                             | superiority                      |
| Method                                                                                                                    | Wald Confidence Limits           |
| Parameter estimate                                                                                                        | Relative Risk (RR)               |
| Point estimate                                                                                                            | 1.01                             |
| Confidence interval                                                                                                       |                                  |
| level                                                                                                                     | 95 %                             |
| sides                                                                                                                     | 2-sided                          |
| lower limit                                                                                                               | 0.15                             |
| upper limit                                                                                                               | 6.96                             |



|                                                                                      |                                |
|--------------------------------------------------------------------------------------|--------------------------------|
| <b>Statistical analysis title</b>                                                    | Milvexian 200 mg BID           |
| Statistical analysis description:                                                    |                                |
| Wald Confidence Limits. 95% CIs for RR are constructed using Wald Confidence Limits. |                                |
| Comparison groups                                                                    | Placebo v Milvexian 200 mg BID |
| Number of subjects included in analysis                                              | 1042                           |
| Analysis specification                                                               | Pre-specified                  |
| Analysis type                                                                        | superiority                    |
| Method                                                                               | Wald Confidence Limits         |
| Parameter estimate                                                                   | Relative Risk (RR)             |
| Point estimate                                                                       | 1.4                            |
| Confidence interval                                                                  |                                |
| level                                                                                | 95 %                           |
| sides                                                                                | 2-sided                        |
| lower limit                                                                          | 0.87                           |
| upper limit                                                                          | 2.25                           |

|                                                                                      |                                 |
|--------------------------------------------------------------------------------------|---------------------------------|
| <b>Statistical analysis title</b>                                                    | Milvexian 50 mg QD over Placebo |
| Statistical analysis description:                                                    |                                 |
| Wald Confidence Limits. 95% CIs for RR are constructed using Wald Confidence Limits. |                                 |
| Comparison groups                                                                    | Placebo v Milvexian 50 mg QD    |
| Number of subjects included in analysis                                              | 713                             |
| Analysis specification                                                               | Pre-specified                   |
| Analysis type                                                                        | superiority                     |
| Method                                                                               | Wald Confidence Limits          |
| Parameter estimate                                                                   | Relative Risk (RR)              |
| Point estimate                                                                       | 2.48                            |
| Confidence interval                                                                  |                                 |
| level                                                                                | 95 %                            |
| sides                                                                                | 2-sided                         |
| lower limit                                                                          | 0.83                            |
| upper limit                                                                          | 7.42                            |

|                                                                                      |                                  |
|--------------------------------------------------------------------------------------|----------------------------------|
| <b>Statistical analysis title</b>                                                    | Milvexian 25 mg BID over Placebo |
| Statistical analysis description:                                                    |                                  |
| Wald Confidence Limits. 95% CIs for RR are constructed using Wald Confidence Limits. |                                  |
| Comparison groups                                                                    | Placebo v Milvexian 25 mg BID    |
| Number of subjects included in analysis                                              | 1009                             |
| Analysis specification                                                               | Pre-specified                    |
| Analysis type                                                                        | superiority                      |
| Method                                                                               | Wald Confidence Limits           |
| Parameter estimate                                                                   | Relative Risk (RR)               |
| Point estimate                                                                       | 0.69                             |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.36    |
| upper limit         | 1.3     |

|                                   |                                   |
|-----------------------------------|-----------------------------------|
| <b>Statistical analysis title</b> | Milvexian 100 mg BID over Placebo |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

Wald Confidence Limits. 95% CIs for RR are constructed using Wald Confidence Limits.

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Comparison groups                       | Placebo v Milvexian 100 mg BID |
| Number of subjects included in analysis | 1001                           |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| Method                                  | Wald Confidence Limits         |
| Parameter estimate                      | Relative Risk (RR)             |
| Point estimate                          | 0.65                           |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.33    |
| upper limit         | 1.25    |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

SAEs and NSAEs were assessed from first dose to 7 days after last dose of study therapy (up to approximately 112 days).

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Placebo + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Placebo + Aspirin 100 mg QD on days 22-90. All administered orally.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Milvexian 25 mg QD |
|-----------------------|--------------------|

Reporting group description:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Milvexian 50 mg QD |
|-----------------------|--------------------|

Reporting group description:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Milvexian 100 mg QD |
|-----------------------|---------------------|

Reporting group description:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg QD + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg QD + Aspirin 100 mg QD on days 22-90. All administered orally.

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Milvexian 50 mg BID |
|-----------------------|---------------------|

Reporting group description:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 50 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 50 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Milvexian 25 mg BID |
|-----------------------|---------------------|

Reporting group description:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 25 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 25 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Milvexian 100 mg BID |
|-----------------------|----------------------|

Reporting group description:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 100 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 100 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Milvexian 200 mg BID |
|-----------------------|----------------------|

Reporting group description:

Loading dose of Clopidogrel 300 mg + Aspirin 100 mg followed by Milvexian 200 mg BID + Aspirin 100 mg QD + Clopidogrel 75 mg QD on days 1-21 and Milvexian 200 mg BID + Aspirin 100 mg QD on days 22-90. All administered orally.

| <b>Serious adverse events</b>                                       | Placebo           | Milvexian 25 mg QD | Milvexian 50 mg QD |
|---------------------------------------------------------------------|-------------------|--------------------|--------------------|
| Total subjects affected by serious adverse events                   |                   |                    |                    |
| subjects affected / exposed                                         | 94 / 682 (13.78%) | 37 / 325 (11.38%)  | 5 / 22 (22.73%)    |
| number of deaths (all causes)                                       | 5                 | 4                  | 0                  |
| number of deaths resulting from adverse events                      |                   |                    |                    |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                    |                    |
| Colon cancer                                                        |                   |                    |                    |
| subjects affected / exposed                                         | 0 / 682 (0.00%)   | 1 / 325 (0.31%)    | 0 / 22 (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              |
| Breast cancer                                                       |                   |                    |                    |
| subjects affected / exposed                                         | 0 / 682 (0.00%)   | 0 / 325 (0.00%)    | 0 / 22 (0.00%)     |
| 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-cell lymphoma                                                     |                   |                    |                    |
| subjects affected / exposed                                         | 0 / 682 (0.00%)   | 0 / 325 (0.00%)    | 0 / 22 (0.00%)     |
| 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 / 682 (0.00%)   | 0 / 325 (0.00%)    | 0 / 22 (0.00%)     |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 0              | 0 / 0              |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0              | 0 / 0              |
| Invasive ductal breast carcinoma                                    |                   |                    |                    |
| subjects affected / exposed                                         | 0 / 682 (0.00%)   | 0 / 325 (0.00%)    | 0 / 22 (0.00%)     |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 0              | 0 / 0              |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0              | 0 / 0              |
| Lung neoplasm malignant                                             |                   |                    |                    |
| subjects affected / exposed                                         | 0 / 682 (0.00%)   | 0 / 325 (0.00%)    | 0 / 22 (0.00%)     |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 0              | 0 / 0              |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0              | 0 / 0              |
| Metastases to lung                                                  |                   |                    |                    |
| subjects affected / exposed                                         | 0 / 682 (0.00%)   | 1 / 325 (0.31%)    | 0 / 22 (0.00%)     |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1              | 0 / 0              |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 1              | 0 / 0              |

|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| Metastatic neoplasm                             |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Sinonasal papilloma                             |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 1 / 325 (0.31%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Squamous cell carcinoma of lung                 |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| 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                              |                 |                 |                |
| Deep vein thrombosis                            |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hypertension                                    |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Peripheral arterial occlusive disease           |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 1 / 325 (0.31%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0          |
| Orthostatic hypotension                         |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Malignant hypertension                          |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Peripheral artery thrombosis                    |                 |                 |                |

|                                                      |                 |                 |                |
|------------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed                          | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| General disorders and administration site conditions |                 |                 |                |
| Pyrexia                                              |                 |                 |                |
| subjects affected / exposed                          | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Asthenia                                             |                 |                 |                |
| subjects affected / exposed                          | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Sudden cardiac death                                 |                 |                 |                |
| subjects affected / exposed                          | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Reproductive system and breast disorders             |                 |                 |                |
| Benign prostatic hyperplasia                         |                 |                 |                |
| subjects affected / exposed                          | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| 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      |                 |                 |                |
| Pulmonary oedema                                     |                 |                 |                |
| subjects affected / exposed                          | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Pulmonary embolism                                   |                 |                 |                |
| subjects affected / exposed                          | 0 / 682 (0.00%) | 1 / 325 (0.31%) | 0 / 22 (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          |
| Pleural effusion                                     |                 |                 |                |

|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Dyspnoea                                        |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 1 / 325 (0.31%) | 0 / 22 (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 respiratory failure                       |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Respiratory failure                             |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 1 / 325 (0.31%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0          |
| Psychiatric disorders                           |                 |                 |                |
| Anxiety disorder                                |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Mania                                           |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| 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                                  |                 |                 |                |
| Activated partial thromboplastin time prolonged |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Ejection fraction decreased                     |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |

|                                                              |                 |                 |                |
|--------------------------------------------------------------|-----------------|-----------------|----------------|
| Liver function test increased<br>subjects affected / exposed | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to<br>treatment / all           | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           | 0 / 0          |
| Injury, poisoning and procedural<br>complications            |                 |                 |                |
| Accidental overdose                                          |                 |                 |                |
| subjects affected / exposed                                  | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to<br>treatment / all           | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           | 0 / 0          |
| Cystitis radiation                                           |                 |                 |                |
| subjects affected / exposed                                  | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to<br>treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           | 0 / 0          |
| Forearm fracture                                             |                 |                 |                |
| subjects affected / exposed                                  | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to<br>treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           | 0 / 0          |
| Fibula fracture                                              |                 |                 |                |
| subjects affected / exposed                                  | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to<br>treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           | 0 / 0          |
| Femur fracture                                               |                 |                 |                |
| subjects affected / exposed                                  | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to<br>treatment / all           | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           | 0 / 0          |
| Post procedural haemorrhage                                  |                 |                 |                |
| subjects affected / exposed                                  | 0 / 682 (0.00%) | 1 / 325 (0.31%) | 0 / 22 (0.00%) |
| occurrences causally related to<br>treatment / all           | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           | 0 / 0          |
| Procedural haemorrhage                                       |                 |                 |                |
| subjects affected / exposed                                  | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to<br>treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           | 0 / 0          |



|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| Post procedural stroke                          |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Reactive gastropathy                            |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Radius fracture                                 |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Skin laceration                                 |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 1 / 325 (0.31%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Subdural haematoma                              |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Congenital, familial and genetic disorders      |                 |                 |                |
| Atrial septal defect                            |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 1 / 325 (0.31%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cardiac disorders                               |                 |                 |                |
| Acute myocardial infarction                     |                 |                 |                |
| subjects affected / exposed                     | 2 / 682 (0.29%) | 0 / 325 (0.00%) | 1 / 22 (4.55%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Atrial fibrillation                             |                 |                 |                |
| subjects affected / exposed                     | 4 / 682 (0.59%) | 3 / 325 (0.92%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 3           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |

|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| Angina unstable                                 |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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 pectoris                                 |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 1 / 325 (0.31%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Atrial flutter                                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 1 / 325 (0.31%) | 0 / 22 (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          |
| Atrial tachycardia                              |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| 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                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Atrioventricular block second degree            |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cardiac failure                                 |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cardiac arrest                                  |                 |                 |                |
| subjects affected / exposed                     | 2 / 682 (0.29%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Bradycardia                                     |                 |                 |                |

|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cardiac failure acute                           |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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 failure congestive                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Intracardiac thrombus                           |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| 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                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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 ventricular thrombosis                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 1 / 325 (0.31%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Ischaemic cardiomyopathy                        |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Prinzmetal angina                               |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Nodal rhythm                                    |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| 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 ischaemia                            |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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 / 682 (0.00%) | 1 / 325 (0.31%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Sinus tachycardia                               |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 1 / 325 (0.31%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Nervous system disorders                        |                 |                 |                |
| Basilar artery occlusion                        |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Basilar artery stenosis                         |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Aphasia                                         |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Basilar migraine                                |                 |                 |                |

|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Carotid artery thrombosis                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cerebral infarction                             |                 |                 |                |
| subjects affected / exposed                     | 4 / 682 (0.59%) | 1 / 325 (0.31%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Cerebral ischaemia                              |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Cerebral venous thrombosis                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Brain stem stroke                               |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Carotid artery stenosis                         |                 |                 |                |
| subjects affected / exposed                     | 4 / 682 (0.59%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Epilepsy                                        |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 1 / 325 (0.31%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Encephalopathy                                  |                 |                 |                |

|                                                 |                  |                 |                 |
|-------------------------------------------------|------------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 682 (0.00%)  | 0 / 325 (0.00%) | 0 / 22 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| Embolitic cerebral infarction                   |                  |                 |                 |
| subjects affected / exposed                     | 0 / 682 (0.00%)  | 0 / 325 (0.00%) | 0 / 22 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| Dementia                                        |                  |                 |                 |
| subjects affected / exposed                     | 0 / 682 (0.00%)  | 0 / 325 (0.00%) | 0 / 22 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| Dysarthria                                      |                  |                 |                 |
| subjects affected / exposed                     | 0 / 682 (0.00%)  | 1 / 325 (0.31%) | 0 / 22 (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           |
| Focal dyscognitive seizures                     |                  |                 |                 |
| subjects affected / exposed                     | 0 / 682 (0.00%)  | 0 / 325 (0.00%) | 0 / 22 (0.00%)  |
| 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                     | 21 / 682 (3.08%) | 9 / 325 (2.77%) | 3 / 22 (13.64%) |
| occurrences causally related to treatment / all | 0 / 21           | 0 / 9           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| Ischaemic cerebral infarction                   |                  |                 |                 |
| subjects affected / exposed                     | 3 / 682 (0.44%)  | 1 / 325 (0.31%) | 0 / 22 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| Intracranial aneurysm                           |                  |                 |                 |
| subjects affected / exposed                     | 0 / 682 (0.00%)  | 1 / 325 (0.31%) | 0 / 22 (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           |
| Haemorrhagic transformation stroke              |                  |                 |                 |

|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Generalised tonic-clonic seizure                |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Lacunar stroke                                  |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Mental impairment                               |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Myasthenia gravis crisis                        |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Myelopathy                                      |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Neurological symptom                            |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Partial seizures                                |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Peroneal nerve palsy                            |                 |                 |                |

|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Pseudostroke                                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Sedation complication                           |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Seizure                                         |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Stroke in evolution                             |                 |                 |                |
| subjects affected / exposed                     | 5 / 682 (0.73%) | 2 / 325 (0.62%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Syncope                                         |                 |                 |                |
| subjects affected / exposed                     | 2 / 682 (0.29%) | 1 / 325 (0.31%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Toxic encephalopathy                            |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 1 / 325 (0.31%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Vertebral artery dissection                     |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Transient ischaemic attack                      |                 |                 |                |



|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 8 / 682 (1.17%) | 1 / 325 (0.31%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 8           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Blood and lymphatic system disorders            |                 |                 |                |
| Anaemia                                         |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 1 / 325 (0.31%) | 0 / 22 (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          |
| Ear and labyrinth disorders                     |                 |                 |                |
| Vertigo positional                              |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Vertigo                                         |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Eye disorders                                   |                 |                 |                |
| Retinal detachment                              |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| 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                      |                 |                 |                |
| Diverticulum intestinal haemorrhagic            |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Duodenal ulcer                                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 1 / 325 (0.31%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastrointestinal haemorrhage                    |                 |                 |                |

|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastric ulcer haemorrhage                       |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 1 / 325 (0.31%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Faecaloma                                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Duodenal ulcer perforation                      |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Duodenal ulcer haemorrhage                      |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Haemorrhoidal haemorrhage                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Peptic ulcer haemorrhage                        |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pancreatitis acute                              |                 |                 |                |
| subjects affected / exposed                     | 2 / 682 (0.29%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Oesophagitis haemorrhagic                       |                 |                 |                |

|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Nausea                                          |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Mallory-Weiss syndrome                          |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| 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 gastrointestinal haemorrhage              |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Small intestinal haemorrhage                    |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| 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 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| 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                         |                 |                 |                |
| Cholelithiasis                                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cholecystitis acute                             |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cholecystitis                                   |                 |                 |                |

|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 2 / 682 (0.29%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hepatitis fulminant                             |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Skin and subcutaneous tissue disorders          |                 |                 |                |
| Diabetic foot                                   |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Drug eruption                                   |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 1 / 325 (0.31%) | 0 / 22 (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          |
| Rash macular                                    |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Toxic epidermal necrolysis                      |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 1 / 22 (4.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Urticaria                                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| 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                     |                 |                 |                |
| Cystitis haemorrhagic                           |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| 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                     | 3 / 682 (0.44%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Renal tubular necrosis                          |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Renal failure                                   |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Prerenal failure                                |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Nephropathy toxic                               |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Haematuria                                      |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| 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 |                 |                 |                |
| Musculoskeletal chest pain                      |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| 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 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| 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                     |                 |                 |                |

|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| Arthritis bacterial                             |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Bronchitis                                      |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 1 / 325 (0.31%) | 0 / 22 (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          |
| COVID-19                                        |                 |                 |                |
| subjects affected / exposed                     | 5 / 682 (0.73%) | 2 / 325 (0.62%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cellulitis                                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Clostridium difficile infection                 |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 1 / 325 (0.31%) | 0 / 22 (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          |
| Cystitis                                        |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Diverticulitis                                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Diverticulitis intestinal perforated            |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Febrile infection                               |                 |                 |                |

|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastroenteritis                                 |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Osteomyelitis                                   |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Large intestine infection                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 1 / 325 (0.31%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0          |
| Infected dermal cyst                            |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Pneumonia                                       |                 |                 |                |
| subjects affected / exposed                     | 3 / 682 (0.44%) | 0 / 325 (0.00%) | 1 / 22 (4.55%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pneumonia aspiration                            |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Sepsis                                          |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Septic shock                                    |                 |                 |                |

|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Staphylococcal bacteraemia                      |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Tuberculosis                                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Urinary tract infection                         |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 2 / 325 (0.62%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Wound infection pseudomonas                     |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| 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                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Metabolism and nutrition disorders              |                 |                 |                |
| Dehydration                                     |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hyperglycaemia                                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hyperkalaemia                                   |                 |                 |                |



|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 682 (0.00%) | 1 / 325 (0.31%) | 0 / 22 (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          |
| Hypoglycaemia                                   |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hyponatraemia                                   |                 |                 |                |
| subjects affected / exposed                     | 1 / 682 (0.15%) | 0 / 325 (0.00%) | 0 / 22 (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          |
| Type 2 diabetes mellitus                        |                 |                 |                |
| subjects affected / exposed                     | 0 / 682 (0.00%) | 0 / 325 (0.00%) | 0 / 22 (0.00%) |
| 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>                                       | Milvexian 100 mg QD | Milvexian 50 mg BID | Milvexian 25 mg BID |
|---------------------------------------------------------------------|---------------------|---------------------|---------------------|
| Total subjects affected by serious adverse events                   |                     |                     |                     |
| subjects affected / exposed                                         | 3 / 17 (17.65%)     | 41 / 325 (12.62%)   | 39 / 313 (12.46%)   |
| number of deaths (all causes)                                       | 0                   | 3                   | 3                   |
| number of deaths resulting from adverse events                      |                     |                     |                     |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                     |                     |                     |
| Colon cancer                                                        |                     |                     |                     |
| subjects affected / exposed                                         | 0 / 17 (0.00%)      | 0 / 325 (0.00%)     | 0 / 313 (0.00%)     |
| occurrences causally related to treatment / all                     | 0 / 0               | 0 / 0               | 0 / 0               |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 0               | 0 / 0               |
| Breast cancer                                                       |                     |                     |                     |
| subjects affected / exposed                                         | 0 / 17 (0.00%)      | 0 / 325 (0.00%)     | 0 / 313 (0.00%)     |
| 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-cell lymphoma                                                     |                     |                     |                     |
| subjects affected / exposed                                         | 0 / 17 (0.00%)      | 0 / 325 (0.00%)     | 1 / 313 (0.32%)     |
| occurrences causally related to treatment / all                     | 0 / 0               | 0 / 0               | 0 / 1               |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 0               | 0 / 0               |

|                                                 |                |                 |                 |
|-------------------------------------------------|----------------|-----------------|-----------------|
| Intestinal adenocarcinoma                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Invasive ductal breast carcinoma                |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Lung neoplasm malignant                         |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Metastases to lung                              |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Metastatic neoplasm                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 1           |
| Sinonasal papilloma                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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                              |                |                 |                 |
| Deep vein thrombosis                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Hypertension                                    |                |                 |                 |

|                                                      |                |                 |                 |
|------------------------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0           |
| Peripheral arterial occlusive disease                |                |                 |                 |
| subjects affected / exposed                          | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0           |
| Malignant hypertension                               |                |                 |                 |
| subjects affected / exposed                          | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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           |
| Peripheral artery thrombosis                         |                |                 |                 |
| subjects affected / exposed                          | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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 |                |                 |                 |
| Pyrexia                                              |                |                 |                 |
| subjects affected / exposed                          | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0           |
| Asthenia                                             |                |                 |                 |
| subjects affected / exposed                          | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0           |
| Sudden cardiac death                                 |                |                 |                 |
| subjects affected / exposed                          | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0           |
| Reproductive system and breast disorders             |                |                 |                 |

|                                                             |                |                 |                 |
|-------------------------------------------------------------|----------------|-----------------|-----------------|
| Benign prostatic hyperplasia<br>subjects affected / exposed | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0          | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders             |                |                 |                 |
| Pulmonary oedema<br>subjects affected / exposed             | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 1 / 313 (0.32%) |
| occurrences causally related to<br>treatment / all          | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all               | 0 / 0          | 0 / 0           | 0 / 0           |
| Pulmonary embolism<br>subjects affected / exposed           | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0          | 0 / 0           | 0 / 0           |
| Pleural effusion<br>subjects affected / exposed             | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0          | 0 / 0           | 0 / 0           |
| Dyspnoea<br>subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0          | 0 / 0           | 0 / 0           |
| Acute respiratory failure<br>subjects affected / exposed    | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0          | 0 / 0           | 0 / 0           |
| Respiratory failure<br>subjects affected / exposed          | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0          | 0 / 0           | 0 / 0           |
| Psychiatric disorders                                       |                |                 |                 |
| Anxiety disorder<br>subjects affected / exposed             | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0          | 0 / 0           | 0 / 0           |

|                                                 |                |                 |                 |
|-------------------------------------------------|----------------|-----------------|-----------------|
| Mania                                           |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Investigations                                  |                |                 |                 |
| Activated partial thromboplastin time prolonged |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Ejection fraction decreased                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Liver function test increased                   |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                |                 |                 |
| Accidental overdose                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Cystitis radiation                              |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Forearm fracture                                |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Fibula fracture                                 |                |                 |                 |

|                                                 |                |                 |                 |
|-------------------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Femur fracture                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Procedural haemorrhage                          |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Post procedural stroke                          |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Reactive gastropathy                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Radius fracture                                 |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Skin laceration                                 |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Subdural haematoma                              |                |                 |                 |

|                                                 |                |                 |                 |
|-------------------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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           |
| Congenital, familial and genetic disorders      |                |                 |                 |
| Atrial septal defect                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                |                 |                 |
| Acute myocardial infarction                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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 / 17 (0.00%) | 0 / 325 (0.00%) | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Angina unstable                                 |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Angina pectoris                                 |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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           |
| Atrial tachycardia                              |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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           |
| Atrioventricular block second degree            |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Cardiac failure                                 |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 2 / 313 (0.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 1           |
| Cardiac arrest                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Bradycardia                                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Cardiac failure acute                           |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Cardiac failure congestive                      |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Intracardiac thrombus                           |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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 ventricular thrombosis                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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 cardiomyopathy                        |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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           |
| Prinzmetal angina                               |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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           |
| Nodal rhythm                                    |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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 ischaemia                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Myocardial infarction                           |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Sinus tachycardia                               |                |                 |                 |

|                                                 |                |                 |                 |
|-------------------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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                        |                |                 |                 |
| Basilar artery occlusion                        |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Basilar artery stenosis                         |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Aphasia                                         |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Basilar migraine                                |                |                 |                 |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 325 (0.00%) | 0 / 313 (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           |
| Carotid artery thrombosis                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Cerebral infarction                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Cerebral ischaemia                              |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Cerebral venous thrombosis                      |                |                 |                 |

|                                                 |                |                 |                 |
|-------------------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Brain stem stroke                               |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Carotid artery stenosis                         |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Epilepsy                                        |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Encephalopathy                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Embolic cerebral infarction                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Dementia                                        |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Dysarthria                                      |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Focal dyscognitive seizures                     |                |                 |                 |

|                                                 |                |                  |                 |
|-------------------------------------------------|----------------|------------------|-----------------|
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%)  | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0            | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0           |
| Ischaemic stroke                                |                |                  |                 |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 10 / 325 (3.08%) | 6 / 313 (1.92%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 10           | 0 / 6           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0           |
| Ischaemic cerebral infarction                   |                |                  |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 2 / 325 (0.62%)  | 3 / 313 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2            | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0           |
| Intracranial aneurysm                           |                |                  |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%)  | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0           |
| Haemorrhagic transformation stroke              |                |                  |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 2 / 325 (0.62%)  | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0           |
| Generalised tonic-clonic seizure                |                |                  |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%)  | 0 / 313 (0.00%) |
| 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 / 17 (0.00%) | 0 / 325 (0.00%)  | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0           |
| Mental impairment                               |                |                  |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%)  | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0           |
| Myasthenia gravis crisis                        |                |                  |                 |

|                                                 |                |                 |                 |
|-------------------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Myelopathy                                      |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Neurological symptom                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Partial seizures                                |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Peroneal nerve palsy                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Pseudostroke                                    |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Sedation complication                           |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Seizure                                         |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Stroke in evolution                             |                |                 |                 |

|                                                 |                |                 |                 |
|-------------------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 17 (5.88%) | 1 / 325 (0.31%) | 4 / 313 (1.28%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Syncope                                         |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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           |
| Toxic encephalopathy                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Vertebral artery dissection                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Transient ischaemic attack                      |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 4 / 313 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                |                 |                 |
| Anaemia                                         |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Ear and labyrinth disorders                     |                |                 |                 |
| Vertigo positional                              |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Vertigo                                         |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 2 / 313 (0.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Eye disorders                                   |                |                 |                 |

|                                                 |                |                 |                 |
|-------------------------------------------------|----------------|-----------------|-----------------|
| Retinal detachment                              |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                |                 |                 |
| Diverticulum intestinal haemorrhagic            |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Duodenal ulcer                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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 haemorrhage                    |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Gastric ulcer haemorrhage                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Faecaloma                                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Duodenal ulcer perforation                      |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Duodenal ulcer haemorrhage                      |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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           |
| Haemorrhoidal haemorrhage                       |                |                 |                 |

|                                                 |                |                 |                 |
|-------------------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Peptic ulcer haemorrhage                        |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Pancreatitis acute                              |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Oesophagitis haemorrhagic                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Nausea                                          |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Mallory-Weiss syndrome                          |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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 gastrointestinal haemorrhage              |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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           |
| Small intestinal haemorrhage                    |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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           |
| Rectal haemorrhage                              |                |                 |                 |



|                                                 |                |                 |                 |
|-------------------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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                         |                |                 |                 |
| Cholelithiasis                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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           |
| Cholecystitis acute                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Cholecystitis                                   |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Hepatitis fulminant                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                |                 |                 |
| Diabetic foot                                   |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 2 / 313 (0.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Drug eruption                                   |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Rash macular                                    |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Toxic epidermal necrolysis                      |                |                 |                 |

|                                                 |                |                 |                 |
|-------------------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Urticaria                                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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                     |                |                 |                 |
| Cystitis haemorrhagic                           |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Acute kidney injury                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0           |
| Renal tubular necrosis                          |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Renal failure                                   |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Prerenal failure                                |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Nephropathy toxic                               |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Haematuria                                      |                |                 |                 |

|                                                        |                |                 |                 |
|--------------------------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed                            | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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>Musculoskeletal and connective tissue disorders</b> |                |                 |                 |
| Musculoskeletal chest pain                             |                |                 |                 |
| subjects affected / exposed                            | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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           |
| <b>Infections and infestations</b>                     |                |                 |                 |
| Arthritis bacterial                                    |                |                 |                 |
| subjects affected / exposed                            | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0           | 0 / 0           |
| Bronchitis                                             |                |                 |                 |
| subjects affected / exposed                            | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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           |
| COVID-19                                               |                |                 |                 |
| subjects affected / exposed                            | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 2 / 313 (0.64%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0           | 0 / 0           |
| Cellulitis                                             |                |                 |                 |
| subjects affected / exposed                            | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0           | 0 / 0           |
| Clostridium difficile infection                        |                |                 |                 |
| subjects affected / exposed                            | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0           | 0 / 0           |

|                                                 |                |                 |                 |
|-------------------------------------------------|----------------|-----------------|-----------------|
| Cystitis                                        |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Diverticulitis                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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           |
| Diverticulitis intestinal perforated            |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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           |
| Febrile infection                               |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Gastroenteritis                                 |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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           |
| Osteomyelitis                                   |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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 infection                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Infected dermal cyst                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Pneumonia                                       |                |                 |                 |

|                                                 |                |                 |                 |
|-------------------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0           |
| Pneumonia aspiration                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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           |
| Sepsis                                          |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Septic shock                                    |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Staphylococcal bacteraemia                      |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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           |
| Tuberculosis                                    |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Urinary tract infection                         |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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           |
| Wound infection pseudomonas                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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           |
| Urosepsis                                       |                |                 |                 |

|                                                 |                |                 |                 |
|-------------------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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>Metabolism and nutrition disorders</b>       |                |                 |                 |
| <b>Dehydration</b>                              |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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>Hyperglycaemia</b>                           |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 325 (0.31%) | 0 / 313 (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           |
| <b>Hyperkalaemia</b>                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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>Hypoglycaemia</b>                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| <b>Hyponatraemia</b>                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 0 / 313 (0.00%) |
| 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>Type 2 diabetes mellitus</b>                 |                |                 |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 325 (0.00%) | 1 / 313 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |

| <b>Serious adverse events</b>                     | Milvexian 100 mg<br>BID | Milvexian 200 mg<br>BID |  |
|---------------------------------------------------|-------------------------|-------------------------|--|
| Total subjects affected by serious adverse events |                         |                         |  |
| subjects affected / exposed                       | 42 / 306 (13.73%)       | 54 / 344 (15.70%)       |  |
| number of deaths (all causes)                     | 5                       | 5                       |  |
| number of deaths resulting from adverse events    |                         |                         |  |

|                                                                     |                 |                 |  |
|---------------------------------------------------------------------|-----------------|-----------------|--|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                 |  |
| Colon cancer                                                        |                 |                 |  |
| subjects affected / exposed                                         | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Breast cancer                                                       |                 |                 |  |
| subjects affected / exposed                                         | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| B-cell lymphoma                                                     |                 |                 |  |
| subjects affected / exposed                                         | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Intestinal adenocarcinoma                                           |                 |                 |  |
| subjects affected / exposed                                         | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Invasive ductal breast carcinoma                                    |                 |                 |  |
| subjects affected / exposed                                         | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Lung neoplasm malignant                                             |                 |                 |  |
| subjects affected / exposed                                         | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Metastases to lung                                                  |                 |                 |  |
| subjects affected / exposed                                         | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Metastatic neoplasm                                                 |                 |                 |  |
| subjects affected / exposed                                         | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Sinonasal papilloma                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (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                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Deep vein thrombosis                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypertension                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral arterial occlusive disease           |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (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 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malignant hypertension                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral artery thrombosis                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| General disorders and administration            |                 |                 |  |



|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| site conditions                                 |                 |                 |  |
| Pyrexia                                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Asthenia                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sudden cardiac death                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Reproductive system and breast disorders        |                 |                 |  |
| Benign prostatic hyperplasia                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Pulmonary oedema                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea                                        |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute respiratory failure                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Anxiety disorder                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mania                                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Activated partial thromboplastin time prolonged |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ejection fraction decreased                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Liver function test increased                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (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  |                 |                 |  |
| Accidental overdose                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cystitis radiation                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Forearm fracture                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fibula fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Femur fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post procedural haemorrhage                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Procedural haemorrhage                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post procedural stroke                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Reactive gastropathy                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Radius fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin laceration                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subdural haematoma                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Congenital, familial and genetic disorders      |                 |                 |  |
| Atrial septal defect                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Acute myocardial infarction                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 3 / 306 (0.98%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina unstable                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Angina pectoris                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial flutter                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial tachycardia                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrioventricular block complete                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrioventricular block second degree            |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac arrest                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bradycardia                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure acute                           |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure congestive                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intracardiac thrombus                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (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                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac ventricular thrombosis                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ischaemic cardiomyopathy                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Prinzmetal angina                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (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 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nodal rhythm                                    |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (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                     | 2 / 306 (0.65%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sinus tachycardia                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (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                        |                 |                 |  |
| Basilar artery occlusion                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Basilar artery stenosis                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aphasia                                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Basilar migraine                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Carotid artery thrombosis                       |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral infarction                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 2 / 344 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral ischaemia                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral venous thrombosis                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Brain stem stroke                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Carotid artery stenosis                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epilepsy                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Encephalopathy                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Embolic cerebral infarction                     |                 |                 |  |



|                                                 |                 |                  |  |
|-------------------------------------------------|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Dementia                                        |                 |                  |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Dysarthria                                      |                 |                  |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Focal dyscognitive seizures                     |                 |                  |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (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                     | 7 / 306 (2.29%) | 11 / 344 (3.20%) |  |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 11           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Ischaemic cerebral infarction                   |                 |                  |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 3 / 344 (0.87%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Intracranial aneurysm                           |                 |                  |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Haemorrhagic transformation stroke              |                 |                  |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Generalised tonic-clonic seizure                |                 |                  |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (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 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mental impairment                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myasthenia gravis crisis                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myelopathy                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neurological symptom                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Partial seizures                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peroneal nerve palsy                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pseudostroke                                    |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sedation complication                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Seizure                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Stroke in evolution                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 8 / 344 (2.33%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Toxic encephalopathy                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vertebral artery dissection                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transient ischaemic attack                      |                 |                 |  |
| subjects affected / exposed                     | 4 / 306 (1.31%) | 4 / 344 (1.16%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Anaemia                                         |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ear and labyrinth disorders                     |                 |                 |  |
| Vertigo positional                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vertigo                                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |
| Retinal detachment                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Diverticulum intestinal haemorrhagic            |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal ulcer                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric ulcer haemorrhage                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 2 / 344 (0.58%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Faecaloma                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal ulcer perforation                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal ulcer haemorrhage                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhoidal haemorrhage                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peptic ulcer haemorrhage                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis acute                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophagitis haemorrhagic                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nausea                                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mallory-Weiss syndrome                          |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper gastrointestinal haemorrhage              |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Small intestinal haemorrhage                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rectal haemorrhage                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Cholelithiasis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis acute                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatitis fulminant                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Diabetic foot                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Drug eruption                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rash macular                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Toxic epidermal necrolysis                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urticaria                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Cystitis haemorrhagic                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (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                     | 0 / 306 (0.00%) | 4 / 344 (1.16%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal tubular necrosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure                                   |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 306 (0.00%) | 2 / 344 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Prerenal failure                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nephropathy toxic                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 2 / 344 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematuria                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Musculoskeletal chest pain                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (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 / 306 (0.00%) | 0 / 344 (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                     |                 |                 |  |
| Arthritis bacterial                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |



|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| COVID-19                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 2 / 344 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridium difficile infection                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cystitis                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulitis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulitis intestinal perforated            |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Febrile infection                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (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 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteomyelitis                                   |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Large intestine infection                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infected dermal cyst                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 306 (0.65%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Pneumonia aspiration                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis                                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Septic shock                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Staphylococcal bacteraemia                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tuberculosis                                    |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 5 / 344 (1.45%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound infection pseudomonas                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urosepsis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperglycaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperkalaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 306 (0.33%) | 1 / 344 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyponatraemia                                   |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Type 2 diabetes mellitus                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 306 (0.00%) | 0 / 344 (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            | Milvexian 25 mg QD | Milvexian 50 mg QD |
|---------------------------------------------------------------------|--------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events               |                    |                    |                    |
| subjects affected / exposed                                         | 178 / 682 (26.10%) | 81 / 325 (24.92%)  | 6 / 22 (27.27%)    |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |                    |
| Melanocytic naevus                                                  |                    |                    |                    |
| subjects affected / exposed                                         | 0 / 682 (0.00%)    | 0 / 325 (0.00%)    | 0 / 22 (0.00%)     |
| occurrences (all)                                                   | 0                  | 0                  | 0                  |
| Vascular disorders                                                  |                    |                    |                    |
| Hypertension                                                        |                    |                    |                    |
| subjects affected / exposed                                         | 56 / 682 (8.21%)   | 21 / 325 (6.46%)   | 0 / 22 (0.00%)     |
| occurrences (all)                                                   | 60                 | 21                 | 0                  |
| Hypotension                                                         |                    |                    |                    |
| subjects affected / exposed                                         | 5 / 682 (0.73%)    | 2 / 325 (0.62%)    | 0 / 22 (0.00%)     |
| occurrences (all)                                                   | 5                  | 2                  | 0                  |
| General disorders and administration site conditions                |                    |                    |                    |
| Thirst                                                              |                    |                    |                    |
| subjects affected / exposed                                         | 1 / 682 (0.15%)    | 0 / 325 (0.00%)    | 0 / 22 (0.00%)     |
| occurrences (all)                                                   | 1                  | 0                  | 0                  |
| Non-cardiac chest pain                                              |                    |                    |                    |
| subjects affected / exposed                                         | 1 / 682 (0.15%)    | 1 / 325 (0.31%)    | 0 / 22 (0.00%)     |
| occurrences (all)                                                   | 1                  | 2                  | 0                  |
| Feeling cold                                                        |                    |                    |                    |
| subjects affected / exposed                                         | 0 / 682 (0.00%)    | 0 / 325 (0.00%)    | 0 / 22 (0.00%)     |
| occurrences (all)                                                   | 0                  | 0                  | 0                  |
| Fatigue                                                             |                    |                    |                    |

|                                                  |                      |                      |                     |
|--------------------------------------------------|----------------------|----------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 6 / 682 (0.88%)<br>6 | 2 / 325 (0.62%)<br>2 | 0 / 22 (0.00%)<br>0 |
| Respiratory, thoracic and mediastinal disorders  |                      |                      |                     |
| Oropharyngeal pain                               |                      |                      |                     |
| subjects affected / exposed                      | 0 / 682 (0.00%)      | 1 / 325 (0.31%)      | 0 / 22 (0.00%)      |
| occurrences (all)                                | 0                    | 1                    | 0                   |
| Epistaxis                                        |                      |                      |                     |
| subjects affected / exposed                      | 10 / 682 (1.47%)     | 2 / 325 (0.62%)      | 2 / 22 (9.09%)      |
| occurrences (all)                                | 12                   | 4                    | 5                   |
| Psychiatric disorders                            |                      |                      |                     |
| Mental status changes                            |                      |                      |                     |
| subjects affected / exposed                      | 0 / 682 (0.00%)      | 0 / 325 (0.00%)      | 0 / 22 (0.00%)      |
| occurrences (all)                                | 0                    | 0                    | 0                   |
| Disorientation                                   |                      |                      |                     |
| subjects affected / exposed                      | 0 / 682 (0.00%)      | 0 / 325 (0.00%)      | 0 / 22 (0.00%)      |
| occurrences (all)                                | 0                    | 0                    | 0                   |
| Depressed mood                                   |                      |                      |                     |
| subjects affected / exposed                      | 0 / 682 (0.00%)      | 0 / 325 (0.00%)      | 0 / 22 (0.00%)      |
| occurrences (all)                                | 0                    | 0                    | 0                   |
| Anxiety                                          |                      |                      |                     |
| subjects affected / exposed                      | 5 / 682 (0.73%)      | 3 / 325 (0.92%)      | 1 / 22 (4.55%)      |
| occurrences (all)                                | 5                    | 3                    | 1                   |
| Investigations                                   |                      |                      |                     |
| Activated partial thromboplastin time prolonged  |                      |                      |                     |
| subjects affected / exposed                      | 0 / 682 (0.00%)      | 0 / 325 (0.00%)      | 0 / 22 (0.00%)      |
| occurrences (all)                                | 0                    | 0                    | 0                   |
| Injury, poisoning and procedural complications   |                      |                      |                     |
| Road traffic accident                            |                      |                      |                     |
| subjects affected / exposed                      | 0 / 682 (0.00%)      | 0 / 325 (0.00%)      | 0 / 22 (0.00%)      |
| occurrences (all)                                | 0                    | 0                    | 0                   |
| Skin abrasion                                    |                      |                      |                     |
| subjects affected / exposed                      | 1 / 682 (0.15%)      | 2 / 325 (0.62%)      | 0 / 22 (0.00%)      |
| occurrences (all)                                | 1                    | 2                    | 0                   |
| Nervous system disorders                         |                      |                      |                     |

|                                      |                  |                  |                 |
|--------------------------------------|------------------|------------------|-----------------|
| Tremor                               |                  |                  |                 |
| subjects affected / exposed          | 3 / 682 (0.44%)  | 0 / 325 (0.00%)  | 0 / 22 (0.00%)  |
| occurrences (all)                    | 3                | 0                | 0               |
| Syncope                              |                  |                  |                 |
| subjects affected / exposed          | 1 / 682 (0.15%)  | 1 / 325 (0.31%)  | 0 / 22 (0.00%)  |
| occurrences (all)                    | 1                | 1                | 0               |
| Paraesthesia                         |                  |                  |                 |
| subjects affected / exposed          | 3 / 682 (0.44%)  | 0 / 325 (0.00%)  | 1 / 22 (4.55%)  |
| occurrences (all)                    | 3                | 0                | 1               |
| Headache                             |                  |                  |                 |
| subjects affected / exposed          | 23 / 682 (3.37%) | 16 / 325 (4.92%) | 3 / 22 (13.64%) |
| occurrences (all)                    | 24               | 16               | 3               |
| Dizziness                            |                  |                  |                 |
| subjects affected / exposed          | 7 / 682 (1.03%)  | 4 / 325 (1.23%)  | 0 / 22 (0.00%)  |
| occurrences (all)                    | 7                | 4                | 0               |
| Blood and lymphatic system disorders |                  |                  |                 |
| Anaemia                              |                  |                  |                 |
| subjects affected / exposed          | 4 / 682 (0.59%)  | 1 / 325 (0.31%)  | 0 / 22 (0.00%)  |
| occurrences (all)                    | 4                | 1                | 0               |
| Leukocytosis                         |                  |                  |                 |
| subjects affected / exposed          | 1 / 682 (0.15%)  | 1 / 325 (0.31%)  | 0 / 22 (0.00%)  |
| occurrences (all)                    | 1                | 1                | 0               |
| Iron deficiency anaemia              |                  |                  |                 |
| subjects affected / exposed          | 1 / 682 (0.15%)  | 0 / 325 (0.00%)  | 0 / 22 (0.00%)  |
| occurrences (all)                    | 1                | 0                | 0               |
| Increased tendency to bruise         |                  |                  |                 |
| subjects affected / exposed          | 2 / 682 (0.29%)  | 0 / 325 (0.00%)  | 0 / 22 (0.00%)  |
| occurrences (all)                    | 2                | 0                | 0               |
| Gastrointestinal disorders           |                  |                  |                 |
| Gingival bleeding                    |                  |                  |                 |
| subjects affected / exposed          | 3 / 682 (0.44%)  | 0 / 325 (0.00%)  | 0 / 22 (0.00%)  |
| occurrences (all)                    | 8                | 0                | 0               |
| Flatulence                           |                  |                  |                 |
| subjects affected / exposed          | 1 / 682 (0.15%)  | 0 / 325 (0.00%)  | 0 / 22 (0.00%)  |
| occurrences (all)                    | 1                | 0                | 0               |
| Constipation                         |                  |                  |                 |

|                                    |                  |                  |                |
|------------------------------------|------------------|------------------|----------------|
| subjects affected / exposed        | 44 / 682 (6.45%) | 22 / 325 (6.77%) | 0 / 22 (0.00%) |
| occurrences (all)                  | 46               | 22               | 0              |
| Abdominal pain                     |                  |                  |                |
| subjects affected / exposed        | 5 / 682 (0.73%)  | 3 / 325 (0.92%)  | 0 / 22 (0.00%) |
| occurrences (all)                  | 5                | 3                | 0              |
| Vomiting                           |                  |                  |                |
| subjects affected / exposed        | 7 / 682 (1.03%)  | 7 / 325 (2.15%)  | 0 / 22 (0.00%) |
| occurrences (all)                  | 7                | 7                | 0              |
| Rectal haemorrhage                 |                  |                  |                |
| subjects affected / exposed        | 1 / 682 (0.15%)  | 0 / 325 (0.00%)  | 2 / 22 (9.09%) |
| occurrences (all)                  | 1                | 0                | 2              |
| Nausea                             |                  |                  |                |
| subjects affected / exposed        | 14 / 682 (2.05%) | 11 / 325 (3.38%) | 1 / 22 (4.55%) |
| occurrences (all)                  | 15               | 12               | 1              |
| Renal and urinary disorders        |                  |                  |                |
| Pollakiuria                        |                  |                  |                |
| subjects affected / exposed        | 2 / 682 (0.29%)  | 1 / 325 (0.31%)  | 0 / 22 (0.00%) |
| occurrences (all)                  | 2                | 1                | 0              |
| Acute kidney injury                |                  |                  |                |
| subjects affected / exposed        | 2 / 682 (0.29%)  | 0 / 325 (0.00%)  | 0 / 22 (0.00%) |
| occurrences (all)                  | 2                | 0                | 0              |
| Infections and infestations        |                  |                  |                |
| Urinary tract infection            |                  |                  |                |
| subjects affected / exposed        | 17 / 682 (2.49%) | 8 / 325 (2.46%)  | 0 / 22 (0.00%) |
| occurrences (all)                  | 19               | 9                | 0              |
| Metabolism and nutrition disorders |                  |                  |                |
| Hypomagnesaemia                    |                  |                  |                |
| subjects affected / exposed        | 1 / 682 (0.15%)  | 0 / 325 (0.00%)  | 0 / 22 (0.00%) |
| occurrences (all)                  | 1                | 0                | 0              |
| Hypocalcaemia                      |                  |                  |                |
| subjects affected / exposed        | 1 / 682 (0.15%)  | 0 / 325 (0.00%)  | 0 / 22 (0.00%) |
| occurrences (all)                  | 1                | 0                | 0              |
| Hyperkalaemia                      |                  |                  |                |
| subjects affected / exposed        | 2 / 682 (0.29%)  | 2 / 325 (0.62%)  | 0 / 22 (0.00%) |
| occurrences (all)                  | 2                | 2                | 0              |

|                                   |                  |                     |                     |
|-----------------------------------|------------------|---------------------|---------------------|
| <b>Non-serious adverse events</b> | Milvexian 100 mg | Milvexian 50 mg BID | Milvexian 25 mg BID |
|-----------------------------------|------------------|---------------------|---------------------|

|                                                                                                                                                                                                                                                                                                                                                 | QD                                                                                                    |                                                                                                          |                                                                                                          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed                                                                                                                                                                                                                                                            | 11 / 17 (64.71%)                                                                                      | 92 / 325 (28.31%)                                                                                        | 83 / 313 (26.52%)                                                                                        |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)<br>Melanocytic naevus<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                   | 1 / 17 (5.88%)<br>1                                                                                   | 0 / 325 (0.00%)<br>0                                                                                     | 0 / 313 (0.00%)<br>0                                                                                     |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypotension<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                   | 2 / 17 (11.76%)<br>3<br><br>1 / 17 (5.88%)<br>1                                                       | 24 / 325 (7.38%)<br>24<br><br>4 / 325 (1.23%)<br>4                                                       | 23 / 313 (7.35%)<br>23<br><br>2 / 313 (0.64%)<br>2                                                       |
| General disorders and administration site conditions<br>Thirst<br>subjects affected / exposed<br>occurrences (all)<br><br>Non-cardiac chest pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Feeling cold<br>subjects affected / exposed<br>occurrences (all)<br><br>Fatigue<br>subjects affected / exposed<br>occurrences (all) | 1 / 17 (5.88%)<br>1<br><br>1 / 17 (5.88%)<br>2<br><br>1 / 17 (5.88%)<br>1<br><br>2 / 17 (11.76%)<br>2 | 0 / 325 (0.00%)<br>0<br><br>2 / 325 (0.62%)<br>2<br><br>0 / 325 (0.00%)<br>0<br><br>1 / 325 (0.31%)<br>1 | 0 / 313 (0.00%)<br>0<br><br>1 / 313 (0.32%)<br>1<br><br>0 / 313 (0.00%)<br>0<br><br>3 / 313 (0.96%)<br>4 |
| Respiratory, thoracic and mediastinal disorders<br>Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Epistaxis<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                  | 1 / 17 (5.88%)<br>1<br><br>0 / 17 (0.00%)<br>0                                                        | 0 / 325 (0.00%)<br>0<br><br>5 / 325 (1.54%)<br>5                                                         | 2 / 313 (0.64%)<br>2<br><br>4 / 313 (1.28%)<br>4                                                         |
| Psychiatric disorders                                                                                                                                                                                                                                                                                                                           |                                                                                                       |                                                                                                          |                                                                                                          |



|                                                                                                                                |                      |                        |                        |
|--------------------------------------------------------------------------------------------------------------------------------|----------------------|------------------------|------------------------|
| Mental status changes<br>subjects affected / exposed<br>occurrences (all)                                                      | 1 / 17 (5.88%)<br>1  | 0 / 325 (0.00%)<br>0   | 0 / 313 (0.00%)<br>0   |
| Disorientation<br>subjects affected / exposed<br>occurrences (all)                                                             | 1 / 17 (5.88%)<br>1  | 0 / 325 (0.00%)<br>0   | 1 / 313 (0.32%)<br>1   |
| Depressed mood<br>subjects affected / exposed<br>occurrences (all)                                                             | 1 / 17 (5.88%)<br>1  | 1 / 325 (0.31%)<br>1   | 2 / 313 (0.64%)<br>2   |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                                                                    | 1 / 17 (5.88%)<br>1  | 3 / 325 (0.92%)<br>3   | 6 / 313 (1.92%)<br>6   |
| Investigations<br>Activated partial thromboplastin time<br>prolonged<br>subjects affected / exposed<br>occurrences (all)       | 1 / 17 (5.88%)<br>1  | 0 / 325 (0.00%)<br>0   | 0 / 313 (0.00%)<br>0   |
| Injury, poisoning and procedural<br>complications<br>Road traffic accident<br>subjects affected / exposed<br>occurrences (all) | 1 / 17 (5.88%)<br>1  | 0 / 325 (0.00%)<br>0   | 0 / 313 (0.00%)<br>0   |
| Skin abrasion<br>subjects affected / exposed<br>occurrences (all)                                                              | 1 / 17 (5.88%)<br>1  | 1 / 325 (0.31%)<br>1   | 3 / 313 (0.96%)<br>3   |
| Nervous system disorders<br>Tremor<br>subjects affected / exposed<br>occurrences (all)                                         | 1 / 17 (5.88%)<br>1  | 0 / 325 (0.00%)<br>0   | 1 / 313 (0.32%)<br>1   |
| Syncope<br>subjects affected / exposed<br>occurrences (all)                                                                    | 1 / 17 (5.88%)<br>1  | 3 / 325 (0.92%)<br>3   | 0 / 313 (0.00%)<br>0   |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                                                               | 2 / 17 (11.76%)<br>2 | 0 / 325 (0.00%)<br>0   | 0 / 313 (0.00%)<br>0   |
| Headache<br>subjects affected / exposed<br>occurrences (all)                                                                   | 1 / 17 (5.88%)<br>1  | 14 / 325 (4.31%)<br>14 | 12 / 313 (3.83%)<br>13 |

|                                                                                  |                      |                        |                        |
|----------------------------------------------------------------------------------|----------------------|------------------------|------------------------|
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 17 (5.88%)<br>1  | 7 / 325 (2.15%)<br>7   | 4 / 313 (1.28%)<br>4   |
| Blood and lymphatic system disorders                                             |                      |                        |                        |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                      | 2 / 17 (11.76%)<br>2 | 2 / 325 (0.62%)<br>2   | 2 / 313 (0.64%)<br>2   |
| Leukocytosis<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 17 (5.88%)<br>1  | 0 / 325 (0.00%)<br>0   | 2 / 313 (0.64%)<br>2   |
| Iron deficiency anaemia<br>subjects affected / exposed<br>occurrences (all)      | 1 / 17 (5.88%)<br>1  | 0 / 325 (0.00%)<br>0   | 0 / 313 (0.00%)<br>0   |
| Increased tendency to bruise<br>subjects affected / exposed<br>occurrences (all) | 1 / 17 (5.88%)<br>1  | 1 / 325 (0.31%)<br>1   | 0 / 313 (0.00%)<br>0   |
| Gastrointestinal disorders                                                       |                      |                        |                        |
| Gingival bleeding<br>subjects affected / exposed<br>occurrences (all)            | 1 / 17 (5.88%)<br>1  | 1 / 325 (0.31%)<br>1   | 0 / 313 (0.00%)<br>0   |
| Flatulence<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 17 (5.88%)<br>1  | 2 / 325 (0.62%)<br>2   | 0 / 313 (0.00%)<br>0   |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                 | 3 / 17 (17.65%)<br>3 | 20 / 325 (6.15%)<br>23 | 17 / 313 (5.43%)<br>17 |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)               | 1 / 17 (5.88%)<br>1  | 1 / 325 (0.31%)<br>1   | 0 / 313 (0.00%)<br>0   |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 17 (5.88%)<br>1  | 3 / 325 (0.92%)<br>3   | 2 / 313 (0.64%)<br>2   |
| Rectal haemorrhage<br>subjects affected / exposed<br>occurrences (all)           | 1 / 17 (5.88%)<br>1  | 1 / 325 (0.31%)<br>1   | 0 / 313 (0.00%)<br>0   |
| Nausea                                                                           |                      |                        |                        |

|                                                  |                      |                      |                      |
|--------------------------------------------------|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 2 / 17 (11.76%)<br>2 | 6 / 325 (1.85%)<br>7 | 6 / 313 (1.92%)<br>6 |
| Renal and urinary disorders                      |                      |                      |                      |
| Pollakiuria                                      |                      |                      |                      |
| subjects affected / exposed                      | 1 / 17 (5.88%)       | 1 / 325 (0.31%)      | 0 / 313 (0.00%)      |
| occurrences (all)                                | 1                    | 1                    | 0                    |
| Acute kidney injury                              |                      |                      |                      |
| subjects affected / exposed                      | 2 / 17 (11.76%)      | 1 / 325 (0.31%)      | 1 / 313 (0.32%)      |
| occurrences (all)                                | 2                    | 1                    | 1                    |
| Infections and infestations                      |                      |                      |                      |
| Urinary tract infection                          |                      |                      |                      |
| subjects affected / exposed                      | 1 / 17 (5.88%)       | 6 / 325 (1.85%)      | 9 / 313 (2.88%)      |
| occurrences (all)                                | 1                    | 6                    | 10                   |
| Metabolism and nutrition disorders               |                      |                      |                      |
| Hypomagnesaemia                                  |                      |                      |                      |
| subjects affected / exposed                      | 1 / 17 (5.88%)       | 0 / 325 (0.00%)      | 0 / 313 (0.00%)      |
| occurrences (all)                                | 1                    | 0                    | 0                    |
| Hypocalcaemia                                    |                      |                      |                      |
| subjects affected / exposed                      | 1 / 17 (5.88%)       | 1 / 325 (0.31%)      | 0 / 313 (0.00%)      |
| occurrences (all)                                | 1                    | 1                    | 0                    |
| Hyperkalaemia                                    |                      |                      |                      |
| subjects affected / exposed                      | 1 / 17 (5.88%)       | 2 / 325 (0.62%)      | 0 / 313 (0.00%)      |
| occurrences (all)                                | 1                    | 2                    | 0                    |

| <b>Non-serious adverse events</b>                                      | Milvexian 100 mg<br>BID | Milvexian 200 mg<br>BID |  |
|------------------------------------------------------------------------|-------------------------|-------------------------|--|
| Total subjects affected by non-serious<br>adverse events               |                         |                         |  |
| subjects affected / exposed                                            | 82 / 306 (26.80%)       | 90 / 344 (26.16%)       |  |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps) |                         |                         |  |
| Melanocytic naevus                                                     |                         |                         |  |
| subjects affected / exposed                                            | 0 / 306 (0.00%)         | 0 / 344 (0.00%)         |  |
| occurrences (all)                                                      | 0                       | 0                       |  |
| Vascular disorders                                                     |                         |                         |  |
| Hypertension                                                           |                         |                         |  |
| subjects affected / exposed                                            | 20 / 306 (6.54%)        | 19 / 344 (5.52%)        |  |
| occurrences (all)                                                      | 20                      | 19                      |  |
| Hypotension                                                            |                         |                         |  |

|                                                         |                      |                      |  |
|---------------------------------------------------------|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)        | 1 / 306 (0.33%)<br>1 | 3 / 344 (0.87%)<br>3 |  |
| General disorders and administration<br>site conditions |                      |                      |  |
| Thirst                                                  |                      |                      |  |
| subjects affected / exposed                             | 0 / 306 (0.00%)      | 1 / 344 (0.29%)      |  |
| occurrences (all)                                       | 0                    | 1                    |  |
| Non-cardiac chest pain                                  |                      |                      |  |
| subjects affected / exposed                             | 1 / 306 (0.33%)      | 0 / 344 (0.00%)      |  |
| occurrences (all)                                       | 1                    | 0                    |  |
| Feeling cold                                            |                      |                      |  |
| subjects affected / exposed                             | 1 / 306 (0.33%)      | 0 / 344 (0.00%)      |  |
| occurrences (all)                                       | 1                    | 0                    |  |
| Fatigue                                                 |                      |                      |  |
| subjects affected / exposed                             | 2 / 306 (0.65%)      | 4 / 344 (1.16%)      |  |
| occurrences (all)                                       | 2                    | 4                    |  |
| Respiratory, thoracic and mediastinal<br>disorders      |                      |                      |  |
| Oropharyngeal pain                                      |                      |                      |  |
| subjects affected / exposed                             | 0 / 306 (0.00%)      | 0 / 344 (0.00%)      |  |
| occurrences (all)                                       | 0                    | 0                    |  |
| Epistaxis                                               |                      |                      |  |
| subjects affected / exposed                             | 4 / 306 (1.31%)      | 6 / 344 (1.74%)      |  |
| occurrences (all)                                       | 5                    | 6                    |  |
| Psychiatric disorders                                   |                      |                      |  |
| Mental status changes                                   |                      |                      |  |
| subjects affected / exposed                             | 0 / 306 (0.00%)      | 0 / 344 (0.00%)      |  |
| occurrences (all)                                       | 0                    | 0                    |  |
| Disorientation                                          |                      |                      |  |
| subjects affected / exposed                             | 1 / 306 (0.33%)      | 0 / 344 (0.00%)      |  |
| occurrences (all)                                       | 1                    | 0                    |  |
| Depressed mood                                          |                      |                      |  |
| subjects affected / exposed                             | 0 / 306 (0.00%)      | 1 / 344 (0.29%)      |  |
| occurrences (all)                                       | 0                    | 1                    |  |
| Anxiety                                                 |                      |                      |  |
| subjects affected / exposed                             | 5 / 306 (1.63%)      | 3 / 344 (0.87%)      |  |
| occurrences (all)                                       | 5                    | 3                    |  |
| Investigations                                          |                      |                      |  |

|                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                        |                                                                                                                                       |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|--|
| Activated partial thromboplastin time prolonged<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                        | 1 / 306 (0.33%)<br>1                                                                                                                   | 0 / 344 (0.00%)<br>0                                                                                                                  |  |
| Injury, poisoning and procedural complications<br>Road traffic accident<br>subjects affected / exposed<br>occurrences (all)<br><br>Skin abrasion<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                       | 0 / 306 (0.00%)<br>0<br><br>1 / 306 (0.33%)<br>1                                                                                       | 0 / 344 (0.00%)<br>0<br><br>1 / 344 (0.29%)<br>1                                                                                      |  |
| Nervous system disorders<br>Tremor<br>subjects affected / exposed<br>occurrences (all)<br><br>Syncope<br>subjects affected / exposed<br>occurrences (all)<br><br>Paraesthesia<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Dizziness<br>subjects affected / exposed<br>occurrences (all) | 1 / 306 (0.33%)<br>1<br><br>0 / 306 (0.00%)<br>0<br><br>1 / 306 (0.33%)<br>1<br><br>12 / 306 (3.92%)<br>13<br><br>5 / 306 (1.63%)<br>5 | 0 / 344 (0.00%)<br>0<br><br>0 / 344 (0.00%)<br>0<br><br>1 / 344 (0.29%)<br>2<br><br>9 / 344 (2.62%)<br>10<br><br>2 / 344 (0.58%)<br>2 |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Leukocytosis<br>subjects affected / exposed<br>occurrences (all)<br><br>Iron deficiency anaemia<br>subjects affected / exposed<br>occurrences (all)                                                                                                             | 5 / 306 (1.63%)<br>5<br><br>1 / 306 (0.33%)<br>1<br><br>0 / 306 (0.00%)<br>0                                                           | 8 / 344 (2.33%)<br>8<br><br>0 / 344 (0.00%)<br>0<br><br>0 / 344 (0.00%)<br>0                                                          |  |

|                                                                                  |                        |                        |  |
|----------------------------------------------------------------------------------|------------------------|------------------------|--|
| Increased tendency to bruise<br>subjects affected / exposed<br>occurrences (all) | 0 / 306 (0.00%)<br>0   | 0 / 344 (0.00%)<br>0   |  |
| Gastrointestinal disorders                                                       |                        |                        |  |
| Gingival bleeding<br>subjects affected / exposed<br>occurrences (all)            | 1 / 306 (0.33%)<br>1   | 1 / 344 (0.29%)<br>1   |  |
| Flatulence<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 306 (0.00%)<br>0   | 0 / 344 (0.00%)<br>0   |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                 | 20 / 306 (6.54%)<br>20 | 24 / 344 (6.98%)<br>24 |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)               | 2 / 306 (0.65%)<br>2   | 1 / 344 (0.29%)<br>1   |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                     | 3 / 306 (0.98%)<br>3   | 3 / 344 (0.87%)<br>3   |  |
| Rectal haemorrhage<br>subjects affected / exposed<br>occurrences (all)           | 1 / 306 (0.33%)<br>1   | 2 / 344 (0.58%)<br>2   |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                       | 11 / 306 (3.59%)<br>13 | 5 / 344 (1.45%)<br>5   |  |
| Renal and urinary disorders                                                      |                        |                        |  |
| Pollakiuria<br>subjects affected / exposed<br>occurrences (all)                  | 2 / 306 (0.65%)<br>2   | 1 / 344 (0.29%)<br>1   |  |
| Acute kidney injury<br>subjects affected / exposed<br>occurrences (all)          | 1 / 306 (0.33%)<br>1   | 9 / 344 (2.62%)<br>9   |  |
| Infections and infestations                                                      |                        |                        |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)      | 11 / 306 (3.59%)<br>11 | 12 / 344 (3.49%)<br>13 |  |
| Metabolism and nutrition disorders                                               |                        |                        |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| Hypomagnesaemia             |                 |                 |  |
| subjects affected / exposed | 0 / 306 (0.00%) | 2 / 344 (0.58%) |  |
| occurrences (all)           | 0               | 2               |  |
| Hypocalcaemia               |                 |                 |  |
| subjects affected / exposed | 0 / 306 (0.00%) | 0 / 344 (0.00%) |  |
| occurrences (all)           | 0               | 0               |  |
| Hyperkalaemia               |                 |                 |  |
| subjects affected / exposed | 3 / 306 (0.98%) | 3 / 344 (0.87%) |  |
| occurrences (all)           | 3               | 3               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                           |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| 24 August 2019  | Removed 3 QD doses groups (lowest 25 mg QD dose is maintained); keeping all BID doses. Title of the protocol was changed to reflect the new design. |
| 09 October 2020 | Updated the milestone requirement for DMC review to decide on inclusion of the 200-mg BID dose arm.                                                 |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported