



## Clinical trial results:

**Efficacy and safety of 3 doses of S 38093 (2, 5 and 20 mg/day) versus placebo in patients with mild to moderate Alzheimer's disease. A 24-week international, multi-centre, randomised, double-blind, placebo-controlled phase IIb study followed by a 24-week extension period.**

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

## Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2010-024626-37 |
| Trial protocol           | DE CZ PT HU BG |
| Global end of trial date | 21 March 2014  |

## Results information

|                                |   |
|--------------------------------|---|
| Result version number          | v2 (current)  |
| This version publication date  | 22 July 2016  |
| First version publication date | 31 July 2015  |
| Version creation reason        | • Correction of full data set<br>Data correction due to a system error in EudraCT – Results |

## Trial information

### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | CL2-38093-011 |
|-----------------------|---------------|

### Additional study identifiers

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

Notes:

## Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Institut de Recherches Internationales Servier (I.R.I.S.)  |
| Sponsor organisation address | 50 rue Carnot, Suresnes, France, 92284   |
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| Scientific contact           | Therapeutic Innovation Pole, Institut de Recherches Internationales Servier, +33 1 55 72 43 66, clinicaltrials@servier.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                       | 17 September 2013 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 17 September 2013 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 21 March 2014     |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this trial was to assess the efficacy and safety of S 38093 versus placebo in patients with mild to moderate Alzheimer's disease (AD).

Protection of trial subjects:

Reasons could lead to premature discontinuation of treatment:

- Adverse event: any medical reason or circumstance justifying the discontinuation of the treatment in the investigator's opinion. The patient was to be withdrawn from the study in case of a repeated demonstration of a QTcF > 500 ms or a delta > 60 ms over baseline (inclusion) value. The following changes in hepatic enzymes should lead to treatment discontinuation of a study participant:

ALAT or ASAT > 8x ULN.

ALAT or ASAT > 5x ULN for more than 2 weeks.

ALAT or ASAT > 3x ULN and total bilirubin > 2x ULN.

ALAT or ASAT > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

- Protocol deviation: in case of a missing informed consent or if there was any deviation that could compromise the patient's safety.

- Lack of efficacy (in the investigator's opinion).

- Non medical reason (e.g. patient's consent withdrawal).

- Lost to follow-up: when the investigator had no news from the patient, s/he had to make every effort to contact him/her, to establish if the study treatment had been discontinued, obtain information on the reason for the treatment discontinuation, and to suggest the patient to come to an end-of-study visit. If all attempts to contact the participant failed, the investigator could then declare the participant "lost to follow-up". The investigator had to document all attempts in the corresponding medical file.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 18 October 2011 |
| 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 | Portugal: 5        |
| Country: Number of subjects enrolled | Czech Republic: 57 |
| Country: Number of subjects enrolled | France: 40         |
| Country: Number of subjects enrolled | Bulgaria: 70       |
| Country: Number of subjects enrolled | Germany: 75        |
| Country: Number of subjects enrolled | Hungary: 48        |

|                                      |                         |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Australia: 43           |
| Country: Number of subjects enrolled | Brazil: 53              |
| Country: Number of subjects enrolled | Chile: 65               |
| Country: Number of subjects enrolled | Mexico: 51              |
| Country: Number of subjects enrolled | Romania: 36             |
| Country: Number of subjects enrolled | Russian Federation: 115 |
| Country: Number of subjects enrolled | South Africa: 53        |
| Worldwide total number of subjects   | 711                     |
| EEA total number of subjects         | 331                     |

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)                      | 112 |
| From 65 to 84 years                       | 588 |
| 85 years and over                         | 11  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Six hundred (600) out-patients aged 55 to 85 years with mild to moderate Alzheimer's disease were to be included and randomly assigned either S 38093 2 mg/day or S 38093 5 mg/day or S 38093 20 mg/day or placebo.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall study (overall period) |
| 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>             | S 38093 2 mg |

Arm description: -

|  |           |
|--|-----------|
| Arm type                               | Test drug |
| Investigational medicinal product name | S 38093   |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

Dosage and administration details:

1 tablet, orally, with a glass of water, once a day, upon waking in the morning.

|                  |              |
|------------------|--------------|
| <b>Arm title</b> | S 38093 5 mg |
|------------------|--------------|

Arm description: -

|  |           |
|--|-----------|
| Arm type                               | Test drug |
| Investigational medicinal product name | S 38093   |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

Dosage and administration details:

1 tablet, orally, with a glass of water, once a day, upon waking in the morning.

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | S 38093 20 mg |
|------------------|---------------|

Arm description: -

|  |           |
|--|-----------|
| Arm type                               | Test drug |
| Investigational medicinal product name | S 38093   |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

Dosage and administration details:

1 tablet, orally, with a glass of water, once a day, upon waking in the morning.

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

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

Dosage and administration details:

One tablet, orally, with a glass of water, once a day, upon waking in the morning.

| <b>Number of subjects in period 1</b> | S 38093 2 mg | S 38093 5 mg | S 38093 20 mg |
|---------------------------------------|--------------|--------------|---------------|
| Started                               | 176          | 175          | 181           |
| Completed                             | 151          | 158          | 162           |
| Not completed                         | 25           | 17           | 19            |
| Adverse event, non-fatal              | 6            | 6            | 7             |
| Non-medical reason                    | 14           | 9            | 8             |
| Protocol deviation                    | 5            | -            | 3             |
| Lack of efficacy                      | -            | 2            | 1             |

| <b>Number of subjects in period 1</b> | Placebo |
|---------------------------------------|---------|
| Started                               | 179     |
| Completed                             | 162     |
| Not completed                         | 17      |
| Adverse event, non-fatal              | 6       |
| Non-medical reason                    | 7       |
| Protocol deviation                    | 4       |
| Lack of efficacy                      | -       |

## Baseline characteristics

### Reporting groups

|                                |               |
|--------------------------------|---------------|
| Reporting group title          | S 38093 2 mg  |
| Reporting group description: - |               |
| Reporting group title          | S 38093 5 mg  |
| Reporting group description: - |               |
| Reporting group title          | S 38093 20 mg |
| Reporting group description: - |               |
| Reporting group title          | Placebo       |
| Reporting group description: - |               |

| Reporting group values                                | S 38093 2 mg | S 38093 5 mg | S 38093 20 mg |
|---|--------------|--------------|---------------|
| Number of subjects                                    | 176          | 175          | 181           |
| 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<br>months)           | 0            | 0            | 0             |
| Children (2-11 years)                                 | 0            | 0            | 0             |
| Adolescents (12-17 years)                             | 0            | 0            | 0             |
| Adults (18-64 years)                                  | 22           | 29           | 27            |
| From 65-84 years                                      | 152          | 142          | 151           |
| 85 years and over                                     | 2            | 4            | 3             |
| Age continuous<br>Units: years                        |              |              |               |
| arithmetic mean                                       | 73           | 71.9         | 72.2          |
| standard deviation                                    | ± 7          | ± 7.2        | ± 7.2         |
| Gender categorical<br>Units: Subjects                 |              |              |               |
| Female  | 101          | 105          | 120           |
| Male  | 75           | 70           | 61            |

| Reporting group values                                | Placebo | Total |  |
|---|---------|-------|--|
| Number of subjects                                    | 179     | 711   |  |
| Age categorical<br>Units: Subjects                    |         |       |  |
| In utero  | 0       | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0       | 0     |  |
| Newborns (0-27 days)                                  | 0       | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0       | 0     |  |
| Children (2-11 years)                                 | 0       | 0     |  |
| Adolescents (12-17 years)                             | 0       | 0     |  |
| Adults (18-64 years)                                  | 34      | 112   |  |
| From 65-84 years                                      | 143     | 588   |  |

|                   |   |    |  |
|-------------------|---|----|--|
| 85 years and over | 2 | 11 |  |
|-------------------|---|----|--|

|                    |       |     |  |
|--------------------|-------|-----|--|
| Age continuous     |       |     |  |
| Units: years       |       |     |  |
| arithmetic mean    | 71.4  |     |  |
| standard deviation | ± 7.2 | -   |  |
| Gender categorical |       |     |  |
| Units: Subjects    |       |     |  |
| Female             | 116   | 442 |  |
| Male               | 63    | 269 |  |

## End points

### End points reporting groups

|  |                    |
|--|--------------------|
| Reporting group title  | S 38093 2 mg       |
| Reporting group description: -   |                    |
| Reporting group title  | S 38093 5 mg       |
| Reporting group description: -   |                    |
| Reporting group title  | S 38093 20 mg      |
| Reporting group description: -   |                    |
| Reporting group title  | Placebo            |
| Reporting group description: -   |                    |
| Subject analysis set title   | Randomised Set     |
| Subject analysis set type  | Intention-to-treat |
| Subject analysis set description:<br>All included patients were randomised (711 patients). |                    |
| Subject analysis set title   | Full Analysis Set  |
| Subject analysis set type  | Full analysis      |
| Subject analysis set description:<br>Consisted of 690 patients                             |                    |
| Subject analysis set title   | Per Protocol Set   |
| Subject analysis set type  | Per protocol       |
| Subject analysis set description:<br>Consisted of 569 patients                             |                    |
| Subject analysis set title   | Safety Set         |
| Subject analysis set type  | Safety analysis    |
| Subject analysis set description:<br>Consisted of 709 patients.                            |                    |

### Primary: ADAS-Cog total score

|  |                      |
|--|----------------------|
| End point title  | ADAS-Cog total score |
| End point description:<br>To assess the efficacy of 3 fixed doses of S 38093 (2, 5 and 20 mg/ day) versus placebo after 24 weeks of treatment, on cognitive performance measured with the ADAS-Cog 11-item in patients with mild to moderate AD. |                      |
| End point type   | Primary              |
| End point timeframe:<br>From baseline to W24   |                      |

| End point values                     | S 38093 2 mg       | S 38093 5 mg       | S 38093 20 mg      | Placebo            |
|--------------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type                   | Reporting group    | Reporting group    | Reporting group    | Reporting group    |
| Number of subjects analysed          | 153 <sup>[1]</sup> | 161 <sup>[2]</sup> | 166 <sup>[3]</sup> | 161 <sup>[4]</sup> |
| Units: score                         |                    |                    |                    |                    |
| arithmetic mean (standard deviation) | -0.45 (± 5.32)     | 0.1 (± 5.53)       | -0.12 (± 5.22)     | 0.34 (± 5.55)      |

Notes:

[1] - FAS having a value of the change from baseline at W24 of the ADAS-Cog total score

[2] - FAS having a value of the change from baseline at W24 of the ADAS-Cog total score

[3] - FAS having a value of the change from baseline at W24 of the ADAS-Cog total score



**Statistical analyses**

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | S 38093 2 mg vs Placebo               |
| Comparison groups                       | Placebo v S 38093 2 mg                |
| Number of subjects included in analysis | 314                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.47                                |
| Method                                  | Mixed-effects Model Repeated Measures |
| Parameter estimate                      | Ajusted Mean difference               |
| Point estimate                          | -0.84                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -2                                    |
| upper limit                             | 0.32                                  |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.59                                  |

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | S 38093 20 mg vs Placebo              |
| Comparison groups                       | Placebo v S 38093 20 mg               |
| Number of subjects included in analysis | 327                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.835                               |
| Method                                  | Mixed-effects Model Repeated Measures |
| Parameter estimate                      | Ajusted Mean difference               |
| Point estimate                          | -0.63                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -1.78                                 |
| upper limit                             | 0.51                                  |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.58                                  |

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Statistical analysis title</b> | S 38093 5 mg vs Placebo |
| Comparison groups                 | S 38093 5 mg v Placebo  |

|   |                                       |
|---|---------------------------------------|
| Number of subjects included in analysis | 322                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 1                                   |
| Method                                  | Mixed-effects Model Repeated Measures |
| Parameter estimate                      | Ajusted Mean difference               |
| Point estimate                          | -0.27                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -1.42                                 |
| upper limit                             | 0.88                                  |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.59                                  |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

During the 48-week treatment period for S 38093 2mg, 5mg and 20 mg

During the 24-week double-blind treatment period for Placebo

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 16 |
|--------------------|----|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | S 38093 2 mg |
|-----------------------|--------------|

Reporting group description: -

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

Reporting group description: -

|                       |               |
|-----------------------|---------------|
| Reporting group title | S 38093 20 mg |
|-----------------------|---------------|

Reporting group description: -

|                       |              |
|-----------------------|--------------|
| Reporting group title | S 38093 5 mg |
|-----------------------|--------------|

Reporting group description: -

| Serious adverse events  | S 38093 2 mg      | Placebo          | S 38093 20 mg     |
|---|-------------------|------------------|-------------------|
| Total subjects affected by serious adverse events                   |                   |                  |                   |
| subjects affected / exposed   | 26 / 176 (14.77%) | 12 / 178 (6.74%) | 34 / 180 (18.89%) |
| number of deaths (all causes)                                       | 5                 | 0                | 3                 |
| number of deaths resulting from adverse events                      | 0                 | 0                | 0                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                  |                   |
| Basal cell carcinoma  |                   |                  |                   |
| subjects affected / exposed   | 2 / 176 (1.14%)   | 0 / 178 (0.00%)  | 0 / 180 (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             |
| Breast cancer   |                   |                  |                   |
| subjects affected / exposed   | 0 / 176 (0.00%)   | 0 / 178 (0.00%)  | 1 / 180 (0.56%)   |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0            | 0 / 0             |
| Colon cancer  |                   |                  |                   |
| subjects affected / exposed   | 1 / 176 (0.57%)   | 0 / 178 (0.00%)  | 0 / 180 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0            | 0 / 0             |
| deaths causally related to treatment / all                          | 0 / 1             | 0 / 0            | 0 / 0             |
| Colon cancer metastatic   |                   |                  |                   |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pancreatic carcinoma metastatic                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Prostate cancer                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 1 / 178 (0.56%) | 0 / 180 (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           |
| Prostatic adenoma                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rectal adenocarcinoma                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Rectal adenoma                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                              |                 |                 |                 |
| Deep vein thrombosis                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertension                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 1 / 178 (0.56%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypotension                                     |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| 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 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Shock  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Surgical and medical procedures                      |                 |                 |                 |
| Inguinal hernia repair                               |                 |                 |                 |
| subjects affected / exposed                          | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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 |                 |                 |                 |
| Death  |                 |                 |                 |
| subjects affected / exposed                          | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           | 0 / 1           |
| Asthenia   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Chest pain   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperthermia   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Multi-organ failure                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyrexia   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Sudden death                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Abasia  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 1 / 178 (0.56%) | 0 / 180 (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           |
| Reproductive system and breast disorders        |                 |                 |                 |
| Postmenopausal haemorrhage                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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, thoracic and mediastinal disorders |                 |                 |                 |
| Pulmonary embolism                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 2 / 180 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Choking   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dyspnoea  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 176 (0.00%) | 1 / 178 (0.56%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hydropneumothorax                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Pleural effusion                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Pulmonary hypertension                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 1 / 178 (0.56%) | 0 / 180 (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           |
| Psychiatric disorders                           |                 |                 |                 |
| Depression                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 1 / 178 (0.56%) | 7 / 180 (3.89%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 7           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hallucination, visual                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Middle insomnia                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Aggression                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 1 / 178 (0.56%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Confusional state                               |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Delirium  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Delusion  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Depressed mood                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 1 / 178 (0.56%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Disorientation                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Major depression                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Suicidal ideation                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Investigations                                  |                 |                 |                 |
| Blood creatine phosphokinase increased          |                 |                 |                 |
| subjects affected / exposed                     | 2 / 176 (1.14%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Blood lactate dehydrogenase increased           |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood pressure systolic increased               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Electrocardiogram QT prolonged                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Heart rate decreased                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Fall  |                 |                 |                 |
| subjects affected / exposed                     | 5 / 176 (2.84%) | 3 / 178 (1.69%) | 3 / 180 (1.67%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 3           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Contusion                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Femoral neck fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Laceration                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Alcohol poisoning                               |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ankle fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Confusion postoperative                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| 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                     | 1 / 176 (0.57%) | 1 / 178 (0.56%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hand fracture                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Joint dislocation                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Periorbital contusion                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Procedural haemorrhage                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Road traffic accident                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Tendon rupture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wound   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wrist fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cervical vertebral fracture                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 1 / 178 (0.56%) | 0 / 180 (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           |
| Forearm fracture                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 1 / 178 (0.56%) | 0 / 180 (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                     | 0 / 176 (0.00%) | 1 / 178 (0.56%) | 0 / 180 (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           |
| Congenital, familial and genetic disorders      |                 |                 |                 |
| Hypertrophic cardiomyopathy                     |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| 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                               |                 |                 |                 |
| Cardiac failure congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 1 / 178 (0.56%) | 2 / 180 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina unstable                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Aortic valve stenosis                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrioventricular block first degree             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronary artery stenosis                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sinus arrhythmia                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Supraventricular extrasystoles                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Tachycardia                                     |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial fibrillation                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 1 / 178 (0.56%) | 0 / 180 (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           |
| Right ventricular failure                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 1 / 178 (0.56%) | 0 / 180 (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                        |                 |                 |                 |
| Syncope   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dizziness                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| 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 / 176 (0.57%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dementia Alzheimer's type                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Somnolence                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Balance disorder                                |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| 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 occlusion                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebrovascular disorder                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cognitive disorder                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dysarthria                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Extrapyramidal disorder                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Grand mal convulsion                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhagic stroke                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hemiparesis                                     |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Transient ischaemic attack                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ataxia  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 1 / 178 (0.56%) | 0 / 180 (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           |
| Circadian rhythm sleep disorder                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 1 / 178 (0.56%) | 0 / 180 (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           |
| Coordination abnormal                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 1 / 178 (0.56%) | 0 / 180 (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           |
| Mental impairment                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 1 / 178 (0.56%) | 0 / 180 (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           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Autoimmune thrombocytopenia                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Thrombocytopenia                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Ear and labyrinth disorders                     |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Deafness bilateral                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Tinnitus  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye disorders                                   |                 |                 |                 |
| Retinal vein occlusion                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Visual impairment                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 1 / 178 (0.56%) | 0 / 180 (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                      |                 |                 |                 |
| Intestinal obstruction                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vomiting  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Abdominal pain                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diarrhoea                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Dyspepsia                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Enterocolic                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal hypomotility                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ileus   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Inguinal hernia strangulated                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Intestinal perforation                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Melaena   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Pancreatitis acute                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| 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                         |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Cholecystitis chronic                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| 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          |                 |                 |                 |
| Petechiae                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin ulcer                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| 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                     |                 |                 |                 |
| Renal failure acute                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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 incontinence                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Dupuytren's contracture                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Intervertebral disc degeneration                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intervertebral disc protrusion                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| 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 pain                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Trigger finger                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Infections and infestations                     |                 |                 |                 |
| Appendicitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sepsis  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 176 (1.14%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Herpes zoster ophthalmic                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Infected skin ulcer                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lobar pneumonia                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Pelvic abscess                                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Peritonitis                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| 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 bacterial                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyelonephritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 176 (0.57%) | 0 / 178 (0.00%) | 0 / 180 (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           |
| Viral infection                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Neurosyphilis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 1 / 178 (0.56%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Dehydration                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Decreased appetite                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypophagia                                      |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 176 (0.00%) | 0 / 178 (0.00%) | 0 / 180 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Type 2 diabetes mellitus                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 176 (0.00%) | 1 / 178 (0.56%) | 0 / 180 (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>Serious adverse events</b>                                       | S 38093 5 mg      |  |  |
| Total subjects affected by serious adverse events                   |                   |  |  |
| subjects affected / exposed   | 26 / 175 (14.86%) |  |  |
| number of deaths (all causes)                                       | 2                 |  |  |
| number of deaths resulting from adverse events                      | 0                 |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |  |  |
| Basal cell carcinoma  |                   |  |  |
| subjects affected / exposed   | 0 / 175 (0.00%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 0             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |
| Breast cancer   |                   |  |  |
| subjects affected / exposed   | 0 / 175 (0.00%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 0             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |
| Colon cancer  |                   |  |  |
| subjects affected / exposed   | 0 / 175 (0.00%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 0             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |
| Colon cancer metastatic   |                   |  |  |
| subjects affected / exposed   | 0 / 175 (0.00%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 0             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |
| Pancreatic carcinoma metastatic                                     |                   |  |  |
| subjects affected / exposed   | 0 / 175 (0.00%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 0             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Prostate cancer                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Prostatic adenoma                               |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Rectal adenocarcinoma                           |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Rectal adenoma                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vascular disorders                              |                 |  |  |
| Deep vein thrombosis                            |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypertension                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypotension                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Orthostatic hypotension                         |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Shock   |                 |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                          | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Surgical and medical procedures                      |                 |  |  |
| Inguinal hernia repair                               |                 |  |  |
| subjects affected / exposed                          | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Death  |                 |  |  |
| subjects affected / exposed                          | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Asthenia   |                 |  |  |
| subjects affected / exposed                          | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Chest pain   |                 |  |  |
| subjects affected / exposed                          | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Hyperthermia   |                 |  |  |
| subjects affected / exposed                          | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Multi-organ failure                                  |                 |  |  |
| subjects affected / exposed                          | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Pyrexia  |                 |  |  |
| subjects affected / exposed                          | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Sudden death                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Abasia  |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Reproductive system and breast disorders        |                 |  |  |
| Postmenopausal haemorrhage                      |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Pulmonary embolism                              |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Choking   |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dyspnoea  |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hydropneumothorax                               |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pleural effusion                                |                 |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary hypertension                          |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychiatric disorders                           |                 |  |  |
| Depression                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hallucination, visual                           |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Middle insomnia                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Aggression                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Confusional state                               |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Delirium  |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Delusion  |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Depressed mood                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Disorientation                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Major depression                                |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Suicidal ideation                               |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Investigations                                  |                 |  |  |
| Blood creatine phosphokinase increased          |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood lactate dehydrogenase increased           |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood pressure systolic increased               |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Electrocardiogram QT prolonged                  |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Heart rate decreased                            |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| Fall  |                 |  |  |
| subjects affected / exposed                     | 7 / 175 (4.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 7           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Contusion                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Femoral neck fracture                           |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Laceration                                      |                 |  |  |
| subjects affected / exposed                     | 2 / 175 (1.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Alcohol poisoning                               |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ankle fracture                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Confusion postoperative                         |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Femur fracture                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hand fracture                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Joint dislocation                               |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Periorbital contusion                           |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Procedural haemorrhage                          |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Radius fracture                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Road traffic accident                           |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tendon rupture                                  |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Wound   |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Wrist fracture                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cervical vertebral fracture                     |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Forearm fracture                                |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Subdural haematoma                              |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Congenital, familial and genetic disorders      |                 |  |  |
| Hypertrophic cardiomyopathy                     |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Cardiac failure congestive                      |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| Angina unstable                                 |                 |  |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Aortic valve stenosis                           |                 |  |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Atrioventricular block first degree             |                 |  |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Coronary artery stenosis                        |                 |  |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Sinus arrhythmia                                |                 |  |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Supraventricular extrasystoles                  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Tachycardia                                     |                 |  |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Atrial fibrillation                             |                 |  |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Right ventricular failure                       |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nervous system disorders                        |                 |  |  |
| Syncope   |                 |  |  |
| subjects affected / exposed                     | 3 / 175 (1.71%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dizziness                                       |                 |  |  |
| subjects affected / exposed                     | 2 / 175 (1.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ischaemic stroke                                |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dementia Alzheimer's type                       |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Somnolence                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Balance disorder                                |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Carotid artery occlusion                        |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cerebrovascular disorder                        |                 |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cognitive disorder                              |                 |  |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Dysarthria                                      |                 |  |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Extrapyramidal disorder                         |                 |  |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Grand mal convulsion                            |                 |  |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Haemorrhagic stroke                             |                 |  |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Hemiparesis                                     |                 |  |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Transient ischaemic attack                      |                 |  |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Ataxia  |                 |  |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Circadian rhythm sleep disorder                 |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Coordination abnormal                           |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Mental impairment                               |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood and lymphatic system disorders            |                 |  |  |
| Autoimmune thrombocytopenia                     |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Thrombocytopenia                                |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ear and labyrinth disorders                     |                 |  |  |
| Deafness bilateral                              |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tinnitus  |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Eye disorders                                   |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Retinal vein occlusion                          |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Visual impairment                               |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Intestinal obstruction                          |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vomiting  |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Abdominal pain                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Diarrhoea                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dyspepsia                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Enterocoele                                     |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal hypomotility                   |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ileus   |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Inguinal hernia strangulated                    |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intestinal perforation                          |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Melaena   |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pancreatitis acute                              |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| Cholecystitis chronic                           |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skin and subcutaneous tissue disorders          |                 |  |  |
| Petechiae                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skin ulcer                                      |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Renal failure acute                             |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urinary incontinence                            |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Dupuytren's contracture                         |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intervertebral disc degeneration                |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intervertebral disc protrusion                  |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal pain                            |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Trigger finger                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                                   |  |  |
|---|-----------------------------------|--|--|
| Infections and infestations<br>Appendicitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 0 / 175 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Sepsis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                      | 0 / 175 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Herpes zoster ophthalmic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                    | 0 / 175 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Infected skin ulcer<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                         | 1 / 175 (0.57%)<br>0 / 1<br>0 / 0 |  |  |
| Lobar pneumonia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                             | 0 / 175 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Pelvic abscess<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                              | 0 / 175 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Peritonitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                 | 1 / 175 (0.57%)<br>0 / 1<br>0 / 0 |  |  |
| Pneumonia bacterial<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                         | 1 / 175 (0.57%)<br>0 / 1<br>0 / 0 |  |  |
| Pyelonephritis  |                                   |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Viral infection                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Neurosyphilis                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Dehydration                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Decreased appetite                              |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypophagia                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 175 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Type 2 diabetes mellitus                        |                 |  |  |
| subjects affected / exposed                     | 0 / 175 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

Frequency threshold for reporting non-serious adverse events: 3 %

| <b>Non-serious adverse events</b>                     | S 38093 2 mg       | Placebo           | S 38093 20 mg      |
|---|--------------------|-------------------|--------------------|
| Total subjects affected by non-serious adverse events |                    |                   |                    |
| subjects affected / exposed                           | 102 / 176 (57.95%) | 90 / 178 (50.56%) | 126 / 180 (70.00%) |
| Investigations  |                    |                   |                    |
| Blood creatine phosphokinase increased                |                    |                   |                    |
| subjects affected / exposed                           | 7 / 176 (3.98%)    | 3 / 178 (1.69%)   | 5 / 180 (2.78%)    |
| occurrences (all)                                     | 7                  | 3                 | 5                  |
| Injury, poisoning and procedural complications        |                    |                   |                    |
| Fall  |                    |                   |                    |
| subjects affected / exposed                           | 13 / 176 (7.39%)   | 4 / 178 (2.25%)   | 16 / 180 (8.89%)   |
| occurrences (all)                                     | 14                 | 4                 | 23                 |
| Vascular disorders                                    |                    |                   |                    |
| Hypertension  |                    |                   |                    |
| subjects affected / exposed                           | 8 / 176 (4.55%)    | 8 / 178 (4.49%)   | 12 / 180 (6.67%)   |
| occurrences (all)                                     | 9                  | 8                 | 13                 |
| Orthostatic hypotension                               |                    |                   |                    |
| subjects affected / exposed                           | 6 / 176 (3.41%)    | 3 / 178 (1.69%)   | 6 / 180 (3.33%)    |
| occurrences (all)                                     | 6                  | 3                 | 6                  |
| Nervous system disorders                              |                    |                   |                    |
| Dizziness   |                    |                   |                    |
| subjects affected / exposed                           | 3 / 176 (1.70%)    | 4 / 178 (2.25%)   | 7 / 180 (3.89%)    |
| occurrences (all)                                     | 3                  | 5                 | 8                  |
| Headache  |                    |                   |                    |
| subjects affected / exposed                           | 6 / 176 (3.41%)    | 4 / 178 (2.25%)   | 6 / 180 (3.33%)    |
| occurrences (all)                                     | 6                  | 4                 | 8                  |
| Somnolence  |                    |                   |                    |
| subjects affected / exposed                           | 2 / 176 (1.14%)    | 6 / 178 (3.37%)   | 5 / 180 (2.78%)    |
| occurrences (all)                                     | 2                  | 6                 | 5                  |
| Gastrointestinal disorders                            |                    |                   |                    |
| Diarrhoea   |                    |                   |                    |
| subjects affected / exposed                           | 6 / 176 (3.41%)    | 4 / 178 (2.25%)   | 12 / 180 (6.67%)   |
| occurrences (all)                                     | 7                  | 4                 | 12                 |
| Nausea  |                    |                   |                    |
| subjects affected / exposed                           | 1 / 176 (0.57%)    | 3 / 178 (1.69%)   | 7 / 180 (3.89%)    |
| occurrences (all)                                     | 1                  | 3                 | 7                  |
| Psychiatric disorders                                 |                    |                   |                    |

|   |                       |                      |                        |
|---|-----------------------|----------------------|------------------------|
| Depression<br>subjects affected / exposed<br>occurrences (all)  | 2 / 176 (1.14%)<br>2  | 2 / 178 (1.12%)<br>2 | 11 / 180 (6.11%)<br>11 |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)   | 1 / 176 (0.57%)<br>1  | 3 / 178 (1.69%)<br>4 | 8 / 180 (4.44%)<br>9   |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 176 (0.00%)<br>0  | 1 / 178 (0.56%)<br>1 | 5 / 180 (2.78%)<br>5   |
| Renal and urinary disorders<br>Leukocyturia<br>subjects affected / exposed<br>occurrences (all)                 | 9 / 176 (5.11%)<br>9  | 3 / 178 (1.69%)<br>3 | 8 / 180 (4.44%)<br>9   |
| Infections and infestations<br>Bacteriuria<br>subjects affected / exposed<br>occurrences (all)                  | 5 / 176 (2.84%)<br>5  | 5 / 178 (2.81%)<br>5 | 2 / 180 (1.11%)<br>2   |
| Urinary tract infection bacterial<br>subjects affected / exposed<br>occurrences (all)                           | 6 / 176 (3.41%)<br>8  | 3 / 178 (1.69%)<br>3 | 4 / 180 (2.22%)<br>4   |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                                     | 3 / 176 (1.70%)<br>3  | 2 / 178 (1.12%)<br>2 | 8 / 180 (4.44%)<br>8   |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)   | 4 / 176 (2.27%)<br>4  | 0 / 178 (0.00%)<br>0 | 8 / 180 (4.44%)<br>8   |
| Metabolism and nutrition disorders<br>Hypercholesterolaemia<br>subjects affected / exposed<br>occurrences (all) | 9 / 176 (5.11%)<br>9  | 3 / 178 (1.69%)<br>4 | 4 / 180 (2.22%)<br>5   |
| Hypertriglyceridaemia<br>subjects affected / exposed<br>occurrences (all)                                       | 9 / 176 (5.11%)<br>11 | 2 / 178 (1.12%)<br>2 | 7 / 180 (3.89%)<br>9   |

|  |                    |  |  |
|--|--------------------|--|--|
| <b>Non-serious adverse events</b>  | S 38093 5 mg       |  |  |
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 115 / 175 (65.71%) |  |  |



|   |  |  |  |
|---|--|--|--|
| Investigations<br>Blood creatine phosphokinase increased<br>subjects affected / exposed<br>occurrences (all)  | 2 / 175 (1.14%)<br>2   |  |  |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all)  | 15 / 175 (8.57%)<br>16   |  |  |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)<br><br>Orthostatic hypotension<br>subjects affected / exposed<br>occurrences (all)   | 8 / 175 (4.57%)<br>8<br><br>3 / 175 (1.71%)<br>4                             |  |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Somnolence<br>subjects affected / exposed<br>occurrences (all) | 6 / 175 (3.43%)<br>7<br><br>7 / 175 (4.00%)<br>7<br><br>4 / 175 (2.29%)<br>4 |  |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Nausea<br>subjects affected / exposed<br>occurrences (all)   | 3 / 175 (1.71%)<br>3<br><br>5 / 175 (2.86%)<br>5                             |  |  |
| Psychiatric disorders<br>Depression<br>subjects affected / exposed<br>occurrences (all)<br><br>Anxiety  | 4 / 175 (2.29%)<br>4   |  |  |

|  |   |  |  |
|--|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>5 / 175 (2.86%)</p> <p>5</p> <p>7 / 175 (4.00%)</p> <p>7</p>   |  |  |
| <p>Renal and urinary disorders</p> <p>Leukocyturia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>14 / 175 (8.00%)</p> <p>15</p>   |  |  |
| <p>Infections and infestations</p> <p>Bacteriuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Urinary tract infection bacterial</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Urinary tract infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nasopharyngitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>13 / 175 (7.43%)</p> <p>13</p> <p>9 / 175 (5.14%)</p> <p>11</p> <p>7 / 175 (4.00%)</p> <p>10</p> <p>3 / 175 (1.71%)</p> <p>3</p> |  |  |
| <p>Metabolism and nutrition disorders</p> <p>Hypercholesterolaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hypertriglyceridaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>9 / 175 (5.14%)</p> <p>9</p> <p>3 / 175 (1.71%)</p> <p>3</p>   |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 09 September 2011 | Amendment No. 1 was applicable only in Czech Republic. The competent Authorities requested that in addition to be at least in personal contact for 10h per week with the patient and to have known him for at least one year, the informant was also to be either in a common household with the patient or to be in daily contact with him.  |
| 07 December 2011  | Amendment No. 2 concerned all centres in all countries (international amendment). The main changes were: <ul style="list-style-type: none"><li>- Specification of international units for vitamin B12 cut-off levels (in pmol/L instead of pg/mL) in the biological non-inclusion criteria, without change of the cut-off value.</li><li>- Addition of an antidepressant, agomelatine, to the list of forbidden treatments.</li><li>- Further explanations concerning the eligibility of the patient for MMSE were added.</li><li>- Checklist for brain MRI and corresponding MRI non-inclusion criteria had been updated to be adapted to the 1 Tesla machines that were to be used in the study.</li><li>- MDRDs formula had been corrected since there was an error in the initial protocol.</li><li>- Addition of heart rate data collection to the vital signs recorded during the study, using the Automatic Blood Pressure Monitor each time the blood pressure was recorded.</li><li>- For "Surgery for cataract", event that did not require immediate notification, it was specified that it applied only if surgery for cataract was not associated with any worsening after randomisation.</li><li>- DMC was given access to the study treatment via IRS, and was allowed to recommend continuation of the study with modification(s) on study design.</li><li>- Some scale instructions and worksheets were updated to be in line with the versions finally used in the study (the scales concerned were MMSE, ADCS-CGIC, ADAS-Cog, NPI).</li><li>- Additional information on the management of the therapeutics units and dispensing of study treatment.</li><li>- Administrative changes, correction of typing errors and update on logistics.</li></ul> |
| 03 January 2012   | Amendment No. 3, was applicable only in Portugal. The Ethics Committee of Portugal (CEIC) requested that patients previously treated with AChEI and / or memantine and who were non-responders or did not tolerate the treatment, were eligible for selection into the study.   |
| 27 April 2012     | Amendment No. 4, concerned all centres in all countries (international amendment). The objective of this amendment was to allow patients suffering from mild to moderate Alzheimer's disease, with a slightly higher load of concomitant vascular lesions, to participate in this study. Consequently, the non-inclusion criteria of the brain MRI were modified to allow patients with white matter lesions grade 1 and grade 2 (classified according to the Fazekas scale), common in patients with Alzheimer's disease, to be included in the study. In addition, ADAS-Cog wordlists for recall and recognition tasks were corrected. Additional updates (on drug concentration measurements, glossary and definitions) and corrections of typing errors noted in the protocol were also implemented.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The section NSAE presented EAEs on treatment and included SEAEs. The causality and seriousness of reported SAE can be ultimately upgraded by the sponsor. The sponsor took these decisions to be compliant with the existing ICH E3 Clinical Study Report.

Notes: